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Studies on Congestive Circulatory Failure

III. The Relation of Edema to Urinary Chlorides

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Balance studies in chronic congestive circulatory failure showed marked depression of renal excretion of chloride and further depression when the intake of salt was elevated or when fluids were restricted. This defect may not be accompanied by diminished ability to excrete nitrogen. Although cardiac compensation was usually accompanied by chloride diuresis of proportionate degree, in over one-third of the cases there was evidence of excessive hydration without proportionate retention of salt. Although initiated by a cardiac disorder, congestive failure is mediated by disturbances in renal regulatory mechanisms of both salt and water balances suggesting that hormonal effects play a role.

In congestive circulatory failure* there is close relationship between the appearance and disappearance of edema and the amount of sodium chloride ingested.[3] Adequate restriction of salt† in the diet seldom fails to prevent the retention of water; on the other hand, edema accumulates when the intake of salt is not restricted. In most cases restriction must be severe (1.0–0.5 Gm. per day) to produce the desired result. Furthermore, the kidneys of patients suffering from this condition are unable to excrete sodium and chloride efficiently even when they are given an adequate stimulus (artificial elevation of plasma levels of chloride and sodium).[4]

In order further to examine this relation, chronic congestive circulatory failure is viewed not as a disturbance in the function of the heart (although that is usually the primary factor) but as a disturbance in fluid balance, initiated in the heart, but maintained by other less well understood mechanisms. According to this idea, a deficient heart calls into action a secondary mechanism involving the kidneys which produces congestion by retention of water and sodium chloride. The purpose of this report is to call attention to that mechanism in the light of prevailing concepts of pathogenesis, and to attempt an explanation of certain findings inconsistent with these concepts.

Renal blood flow is reduced in congestive failure to values which have been believed sufficient to cause retention of salt, and therefore water.[5] This finding has been advanced as an explanation for the inability of these kidneys to excrete salt efficiently. Decreased filtration

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Most of these studies were made at the Hospital of the Rockefeller Institute. Analysis and compilation of the data and studies on 4 patients were done at Barnes Hospital, Saint Louis, Mo.

* "Congestive heart failure" is not the best description of the syndrome here discussed. The same sequence of events can occur as a result of mechanical obstruction to the inflow of blood into the heart as when the ventricular myocardium has dilated and failed. Starr[1] and Dock[2] have questioned the term, and the author agrees that it is misleading. A somewhat more accurate phrase is "congestive circulatory failure," which can be of cardiac or noncardiac origin. The syndrome is not strictly a cardiac one, being maintained by organs remote from the heart, although caused by inadequate flow of blood through the heart. An understanding of the mechanism of this condition involves considerable attention being directed away from the heart toward other organs which now appear intimately involved.

† "Salt" as used in this report denotes sodium chloride.

of salt by the kidneys, however, does not explain all of the data. Increased tubular reabsorption of salt may also be present. Furthermore, disturbances of the excretion of water are theoretically possible. This report will present data which suggest (a) that the excretion of salt by the kidneys is specifically depressed; (b) that the ability of the kidneys to concentrate salt in the urine is impaired; (c) that the excretion of salt is not always a function of the volume of urine; (d) that many cardiac patients not only retain excess salt (and therefore water), but also appear to retain water specifically more than salt. Extrarenal hormonal influences on the kidneys are believed to account for these electrolyte disturbances.

While exact studies on balances of water and sodium chloride in the body are difficult to perform for long periods, changes can be followed by (a) controlling the intake of fluids and of sodium chloride carefully at constant levels, (b) measuring the urinary excretion of water and sodium chloride, (c) controlling the caloric intake at constant levels in order to maintain body weight, and (d) weighing the subject accurately day by day. Extra water contained in food and produced from its metabolism is relatively constant; variable factors under these circumstances depend upon the water in expired air, and losses of water and sodium chloride through skin and feces. Attempts were therefore made to correlate gains or losses in weight* with the urinary excretion of chlorides and water in cardiac patients undergoing changes in the degree of decompensation and subjected to variations in the intake of sodium chloride or water. The effects of diuretic agents will be reported in a subsequent communication.[6]

* Body weight was considered a much more exact method for measuring changes in fluid content of the body than was the volume of the urine. Fluid is excreted in the urine, in expired air, in perspiration, and in stools. The weight therefore indicates exactly the difference between the intake of water as fluids or food, and the excretion of water in air, perspiration, stools, and urine, disregarding the building up or breaking down of tissues. In short periods of observation (two to four weeks), changes in tissue content were usually negligible, although the results must be interpreted to include them.

Methods

Fifty patients were studied, of whom 30 were men and 20 women. The amount of sodium and chloride in the daily diet was calculated from standard tables.[7] Diets contained constant amounts for long periods. The intake of fluids was rigorously maintained at constant levels. Body weight was carefully measured daily before breakfast to 0.1 Kg. on the same scales. Physical activity was controlled as consistently as possible, patients either remaining in bed throughout the period of study, or being ambulatory in hospital. Control periods often lasted from four to six weeks and some patients remained in hospital for two to five months. Detailed methods of study have been discussed in a previous communication.[3]

Thirty-nine patients exhibited edema and other signs of increased extracellular fluids. Fourteen suffered from rheumatic heart disease, 20 from arteriosclerotic heart disease without arterial hypertension, and 3 from cardiac failure following hypertension. In one, edema resulted from hypoproteinemia, and in one from Cushing's syndrome. Of the 11 patients without edema, 7 suffered from arterial hypertension without disturbance of renal excretory function, 3 from coronary occlusion, and one from mild bronchial asthma. In only the 3 hypertensive individuals and one other was organic renal disease demonstrable by laboratory examination. Nitrogen retention was not present in the remainder, nor was the clearance of urea unduly lower than normal when a state of fluid balance had been achieved. Congestive failure was very severe in most patients, and an attempt was made to study only those cases in which signs and symptoms of congestion were long standing, therapeutic measures had been unsatisfactory, and the primary cardiac disease only slowly progressive.

The total amount of chloride in the urine was measured daily (Volhard-Arnold method), over 2,200 determinations being made. Although technical difficulties of measuring sodium at that time (1937–1941) prevented information being gained concerning the behavior of this ion, measurements of the urinary excretion of chlorides were considered fairly good indications of the fate of salt. There is no evidence that chlorides other than sodium chloride are retained by cardiac patients, or that they play a primary part in edema fluid other than to accompany sodium; on the contrary, chloride ions when administered with other bases (ammonium, potassium) are usually readily excreted. Chloride was therefore calculated as sodium chloride. The urinary volume was carefully collected and measured to as exact values as possible.

Results

The Paradoxical Effect of Ingested Salt on the Urinary Excretion of Chlorides and Water. There

is a critical balance in cardiac patients between the amount of salt ingested in the diet and the accumulation or disappearance of edema. This varies with the nature and extent of the disease from which the patient suffers. For example, when other factors are constant, certain patients will lose edema when the intake of salt is 1.0 Gm. per day and gain it when the intake is 2.0 Gm. A minority require restriction of salt to 0.5 Gm., while less severe cases may be adequately controlled by a dietary intake of 2.0 Gm. Repeated experiments have demonstrated this point. In order to examine the effects of changes in the intake of salt on its excretion, 7 patients were studied for relatively short periods (table 1). In 4 of these patients the urinary excretion of chlorides was actually *depressed* when the intake of salt was at higher levels. This paradoxical effect was accompanied by decreased urinary volume in only two of these, but in three weight was affected unfavorably. In the other 3, slightly more chlorides were excreted when the intake of salt was increased, but the changes were very much

TABLE 1.—*The Effects of Ingested Salt on the Urinary Excretion of Chlorides and Water*

Case No. Date	Intake		Days of Observation	Cl as NaCl		Vol.	Change in Body Weight		Remarks
	NaCl	Fluids		Gm./day	Gm./L.		Total	Gm./day	
	Gm.	*cc.*				*cc.*	*Kg.*		
12. A. J. ♂									
4/ 5/38	1.0	1200	17	.59	.69	853	−0.8	−47	Digitalis given 4/11
4/21/38	0.5	1200	7	.66	.60	1101	−0.2	−86	
8. B. H. ♂									
1/10/39	3.0	1200	10	.69	.98	707	+4.7	+470	
1/20/39	2.0	1200	7	.69	.92	749	+2.7	+386	
1/27/39	1.0	1200	7	.63	.75	840	+0.8	+114	
2/ 4/39	0.5	1200	10	.38	.46	826	+0.3	+29	
16. H. M. ♀									
2/24/38	1.0	800 and 3000	10	1.66	.83	2005	0	0	Intake of fluids varied during experiment
3/ 6/38	2.0	3000	10	1.73	.59	2924	+2.8	+280	
3/26/38	1.0	800 and 3000	10	1.68	1.03	1631	−0.4	−40	
18. E. K. ♂									
11/ 2/37	4.0	1000	8	.16	.40	399	+2.7	+338	
11/10/37	2.0	1000	8	.32	.82	390	+0.3	+38	
35. N. J. ♂									
3/ 8/40	1.0	1500	4	.12	.15	810	−0.4	−100	
3/12/40	5.0	1500	2	.50	.36	1373	−0.3	−150	
3/14/40	1.0	1500	4	.20	.15	1352	+1.4	+350	
7. P. O. ♂									
4/21/39	2.0	1000	7	.17	.18	933	+1.1	+157	
4/28/39	1.0	1000	4	.29	.57	512	+1.8	+450	
39.* C. M. ♂									
4/3 /40	1.5	1500	7	.35	.66	525	−0.1	−14	
4/11/40	4.0	1500	3	.17	.53	320	+2.0	+667	
4/20/40	1.5	1500	5	1.20	.90	1335	−0.4	−80	On digitalis
4/25/40	4.0	1500	7	1.26	1.54	820	+3.4	+486	

* Diagnosis of Case 39, C. M. ♂, age 59. Arteriosclerotic heart disease; coronary occlusion. Other diagnoses given in table 5.

less than expected. Weight in two was gained. Plasma chloride levels were low in the third (N. J.), which may account for the absence of a gain in weight, salt, without water, being retained.

It therefore would appear that ingested salt may act paradoxically on urinary chlorides in certain cardiac patients, serving to depress them; sometimes urine volume is also lowered. Furthermore, when the intake of salt is raised, the expected increase in urinary chlorides does not occur.

The Effect of Injected Salt on Weight and on Urinary Chlorides. When salt in relatively small amounts was injected intravenously in hypertonic solution (4 to 6 per cent) into 3 patients, somewhat similar results were obtained (table 2). The urinary excretion of chlorides was depressed after three of nine injections of relatively small amounts (5.0 to 8.0 Gm.), and after the other 6, was increased only slightly. Body weight was affected unfavorably in two of the subjects. Analyses of individual specimens of urine in one subject (B. H.) showed that the *concentration* of chlorides rose to relatively high levels for a cardiac patient (maximum 31.5 milli-equivalents per liter) immediately after the injection, although the total *amount* excreted was relatively low, and did not change greatly. Larger quantities given by vein (24 to 33 Gm.) caused increases in the concentration and amount of urinary chlorides, but very much less than those seen in normal subjects[4]; the highest values being 70.6, 79.0, 39.5, 36.6, 50.3, and 18.5 m. eq. per L. as compared to normal levels of 178.9, 207.8, and

TABLE 2.—*The Effect of Injected Salt on the Excretion of Chlorides*

Case No. Date	Intake		NaCl Injected*	Days of Observation	Output in Urine			Change in Body Weight	
					Cl as NaCl		Vol.		
	NaCl	Fluids			Gm./day	Gm./L.		Total	Gm./day
	Gm.	*cc.*	*Gm.*				*cc.*	*Kg.*	
8. B. H. ♂									
5/ 1/39	1.0	1200	0	5	.036†	.05	710	+0.5	+100
5/ 6/39			5.0	1	.042	.05	779	+1.7	+340
11/ 1/39	1.0	800	0	5	.45‡	.86	526	−0.5	−100
11/ 6/39			6.0	1	.55	1.30	425	+0.4	+400
11/13/39	1.0	800	6.0	1	.70	1.51	480	+0.5	+500
11/14/39			6.0	1	.28	.76	404	+0.5	+500
11/15/39			6.0	1	.03	.66	423	+0.4	+400
35. N. J. ♂									
4/ 6/40	1.0	1500	0	1	.65	.94	692	−0.4	−400
4/ 7/40			6.0	1	.16	.56	283	−0.2	−200
4/ 8/40			0	4	.12	.18	759	0.0	0
4/12/40			5.0	1	.47	.36	1304	−0.2	−200
4/13/40			5.0	1	.52	.36	1446	−0.1	−100
4/14/40			0	7	.23	.19	1356	+1.2	+174
38.§ P. F. ♂									
3/30/41	1.0	1200	0	5	.03	.06	557	+0.7	+140
4/ 4/41			8.0	1	.10	.12	815	+0.8	+800

* In 4 to 6 per cent solution.

† Plasma chloride 80.2 m. eq./L.

‡ Plasma chloride varied in the next five experiments in this patient as follows (m. eq./L.): 93.4, 97.0, 95.0, 97.5, 101.6.

§ Diagnosis of Case 38, P. F. ♂, age 33. Rheumatic heart disease. Other diagnoses given in table 5.

TABLE 3.—*The Effect of Fluids on the Excretion of Chlorides*

Case No. Date	Intake of Sodium Chloride	Intake of Fluids	Days of Observation	Urinary Excretion of Cl as NaCl		Change in Body Weight	
				Total	Average/day	Total	Gm./day
	Gm.	*cc.*		*Gm.*	*Gm.*	*Kg.*	
8. B. H. ♂							
9/ 6/39	1.0	1200	7	3.84	.55	1.3	186
9/14/39	1.0	2500	19	6.64	.35	2.8	147
10/ 3/39	1.0	2500	14	20.59	1.47	0.1	7
10/18/39	1.0	800	20	14.56	.73	−1.7	−85
20. W. H. ♂							
11/ 1/38	1.0	1200	10	8.11	.81	−0.6	−60
11/11/38	1.0	2000	8	7.94	.99	0.8	100
11/28/38	1.0	600	10	1.84	.18	0.3	30
12/ 8/38	1.0	1200	9	4.60	.51	1.7	189
16. H. M. ♀							
1/21/38	1.0	1500	16	39.60	2.48	−2.9	−181
2/ 6/38	1.0	3000	15	56.70	3.78	−2.6	−173
2/21/38	1.0	800	8	12.30	1.54	−0.4	−50
17. R. L. ♀							
11/ 6/37	2.0	1500	20	24.00	1.20	−2.3	−115
11/26/37	2.0	800	10	11.70	1.17	−1.7	−170
26. A. K. ♂							
9/ 8/39	1.0	1500	12	19.15	1.60	−5.2	−433
9/20/39	1.0	2500	7	11.92	1.70	−2.4	−343
9/27/39	1.0	3000	7	15.76	2.25	−1.8	−257
10/ 4/39	1.0	1000	8	8.84	1.11	−3.7	−463
10/12/39	1.0	2500	19	28.56	1.50	0.9	+47
33. A. M. ♂							
8/29/39	2.0	3500	9	12.65	1.41	3.0	333
9/ 7/39	2.0	2000	9	1.78	.20	2.1	233
19. M. J. ♀							
9/15/37	1.0	1200	9	4.09	.45	1.0	111
9/24/37	1.0	2400	5	1.71	.34	0	0
6. J. B. ♂							
9/14/39	1.0	2400	7	1.93	.28	−0.2	−29
9/21/39	1.0	800	14	3.60	.26	−0.7	−50
10/ 5/39	1.0	1500	13	11.26	0.87	−0.5	−39
18. E. K. ♂							
9/22/37	1.0	3000	7	10.17	1.45	−1.3	−186
9/29/37	1.0	2000	4	3.98	0.99	−0.6	−150
10/ 3/37	1.0	1500	5	8.34	1.67	−1.0	−200
10/ 8/37	1.0	800	7	11.29	1.61	−1.4	−200

See table 5 for diagnoses.

173.8 m. eq. per L. Overloading the circulation with salt did not depress the ability of the kidneys to excrete nitrogen as measured by the clearance of urea and the urea nitrogen level in blood. The very low levels of urinary chlorides accompanied by relatively normal clearances of urea is noteworthy (tables 1, 2, and 3). The presence of edema secondary to

hypoproteinemia was not accompanied by disturbances of the renal excretory mechanisms of salt (fig. 1).

Therefore, it would appear that patients in severe stages of congestive failure are unable to excrete relatively small amounts of chlorides efficiently, whether given by mouth or by vein. These disturbances are probably specifically concerned with the excretion of salt, and bear little relation to the excretion of nitrogen. Depression of urinary excretion of chloride by elevated dietary or parenteral intakes cannot be explained on the basis of reduced glomerular filtration.

The Relation between the Urinary Excretion of Chlorides and the Intake of Salt, in Noncardiac Subjects. Seven patients suffering from a moderate degree of arterial hypertension, and one from mild bronchial asthma were placed on diets containing known amounts of salt, and their urinary chlorides measured daily for four to sixteen days (average nine days). When the daily intake of salt was from 6.0 to 10.4 Gm. (5 subjects), 80.0 to 86.5 per cent of the in-

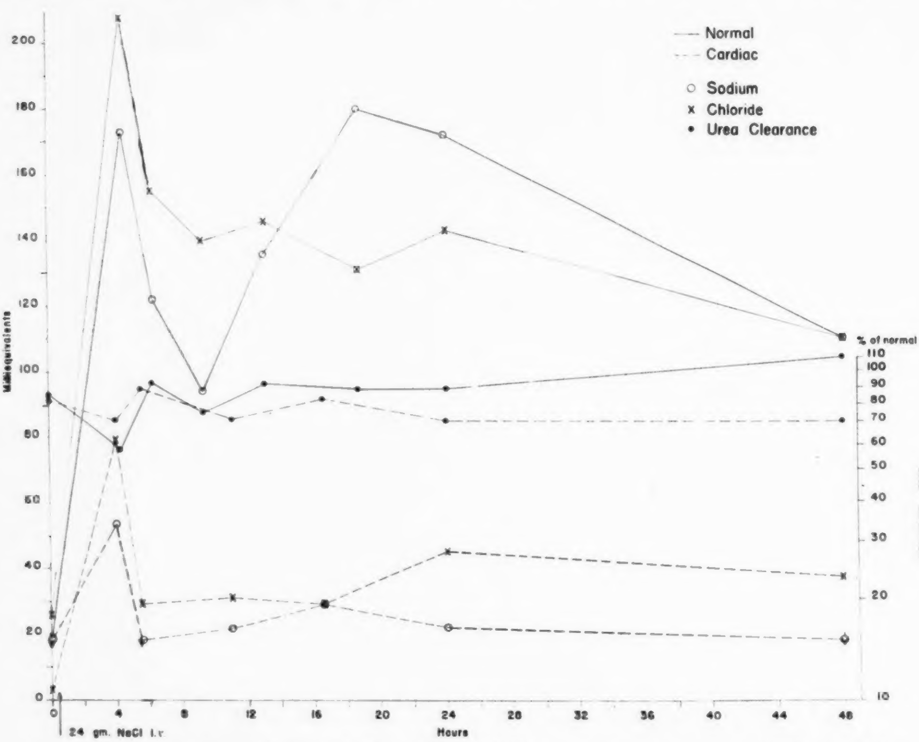


FIG. 1.—Effect of excessive circulating sodium chloride upon urea clearance, and urinary sodium and chloride excretion in a patient with a normal heart, and in one who suffered from congestive circulatory failure which was partially controlled at the time of the experiment. Both patients exhibited approximately the same amount of edema; in the "normal" it was caused by hypoproteinemia probably secondary to ceroid disease, the kidneys being normal as to function and proteinuria. At zero time, 24.0 Gm. of 6 per cent sodium chloride solution was injected intravenously. There was little effect upon urea clearance, but excretion of both sodium and chloride in the cardiac patient was relatively low. Plasma levels of sodium and chloride reached 153 and 119 m. eq. per L., respectively, in the "normal" subject, and 151 and 111 m. eq. per L., respectively, in the cardiac patient. In other similar experiments sodium excretion was too low to measure accurately, values of less than 20 m. eq. per L. being inaccurate (indicated on chart). Data obtained from previous studies.[4]

gested salt was excreted in the urine as chloride (average, 83.6 per cent). When it was 2.0 to 0.5 Gm. (4 subjects), 58.0 to 65.0 per cent was excreted (average, 61.3 per cent). Therefore, chloride losses by other routes than the renal one were affected by a low intake of salt, over five times as much being unaccounted for when the intake was high as when it was low.* Since losses by insensible perspiration were negligible, and patients sweated very little, relatively less depression of the levels in stools than in urine could account for these findings. In cardiac patients losing or gaining edema, this factor cannot be applied to the excretion of urinary chlorides.

The Effects of Changes in the Intake of Fluids upon Urinary Chlorides. Nine patients were studied especially to examine the effect of a relatively high intake of fluids upon the urinary excretion of chlorides. Excessively large amounts of fluids have been reported to be beneficial to certain cardiac patients.[8] When the intake of fluids was raised, no consistent results were seen (table 3). Excessively low intakes (1000 cc. or less per day) were, however, accompanied by decreased excretion of chlorides in 5 of 7 subjects. High intakes (2400 to 3500 cc. per day) initiated a chloride diuresis in 5 of 7 cases, but in only 2 was the intake exceeded, and inconsistencies appeared in the same patient (Cf. B. H., J. B., E. K.). When fluids were suddenly doubled or trebled, a lag period of one to three days was sometimes seen before the urinary volume increased, especially in more severe cases. As weight did not consistently follow chloride excretion, retention of water without chlorides probably occurred in some cases.

From these results it would seem that restriction of fluids in most cardiac patients may depress the urinary excretion of chlorides, while the intake of relatively large volumes may increase them slightly or moderately. Further evidence on this point was obtained from an analysis of the urinary excretion of chlorides during rigid restriction of fluids for twenty-four hours (concentration test). In one patient (H. M.) this procedure, repeated on three separate occasions, was not found to affect the concentration of urinary chlorides appreciably, but the amount excreted became very much less along with the lower urinary output (fig. 2). This was also true in three other cardiac patients on diets containing 1.0 Gm. of salt per day; in a normal individual (G. S.) the concentration increased. Adequate fluids are apparently necessary to allow the kidneys of cardiac patients to excrete chlorides, but excessive amounts are not. Within a certain range, which differs from one patient to another, the excretion of chloride appears to remain fairly constant.

Miscellaneous Observations. The effect of the intravenous injection of large amounts of hypertonic salt solution (24–33 Gm.) on the pulse rate or pulse deficit was observed in 6 subjects. In a normal individual the average pulse rate increased 12 beats per minute the day after the injection; in a cardiac patient with normal rhythm it increased 10. Of 4 subjects exhibiting auricular fibrillation, no change was seen in 2; in the other 2 the rate increased from 60 to 85 and 75 to 100 beats per minute, respectively, and a pulse deficit of slight degree became manifest.

In one, the effects of oxygen upon urinary chloride excretion was studied. Although the patient was not in need of extra oxygen, she was placed in an oxygen chamber at a concentration of 40 to 45 per cent, for five days. The urinary chloride excretion increased from a daily average of 1.40 Gm. during the preceding five days to 1.77 Gm., while urine volume and body weight were not affected.

The content of chlorides in various body fluids was measured in 10 subjects, thirty

* For example, a diet containing 8.0 Gm. of salt given to a normal subject was accompanied by the average daily urinary excretion of 6.45 Gm. of chloride calculated as NaCl, or 80 per cent excretion. When the dietary intake was reduced to 1.0 Gm., the urine contained only 0.63 Gm. after a period of restabilization, or 63 per cent excretion. Average urinary volume was unchanged. Therefore, 1.55 Gm. was excreted in stools (and possibly sweat) on a high intake of salt, and only 0.37 Gm. on a low intake. The stool therefore contained a higher percentage of ingested salt on a low as compared to a high intake. Further restriction of dietary salt caused even larger percentages to be excreted by other than urinary routes.

samples being taken. Protein was measured in eleven samples; as is known, abdominal fluid has the highest concentration (table 4). There was considerable variation in the concentration of chlorides in body fluids, and in progressive samples it sometimes decreased (5 cases) indicating dilution of electrolytes. All of these patients were severely ill and died.

was less, more fluid probably being lost through other routes.

Relation between Weight Loss and Total Chloride Excretion. The total urinary excretion of chlorides for varying periods during which weight was lost (four to sixty-six days) was measured and compared to changes in body weight in 29 cases. The average period of

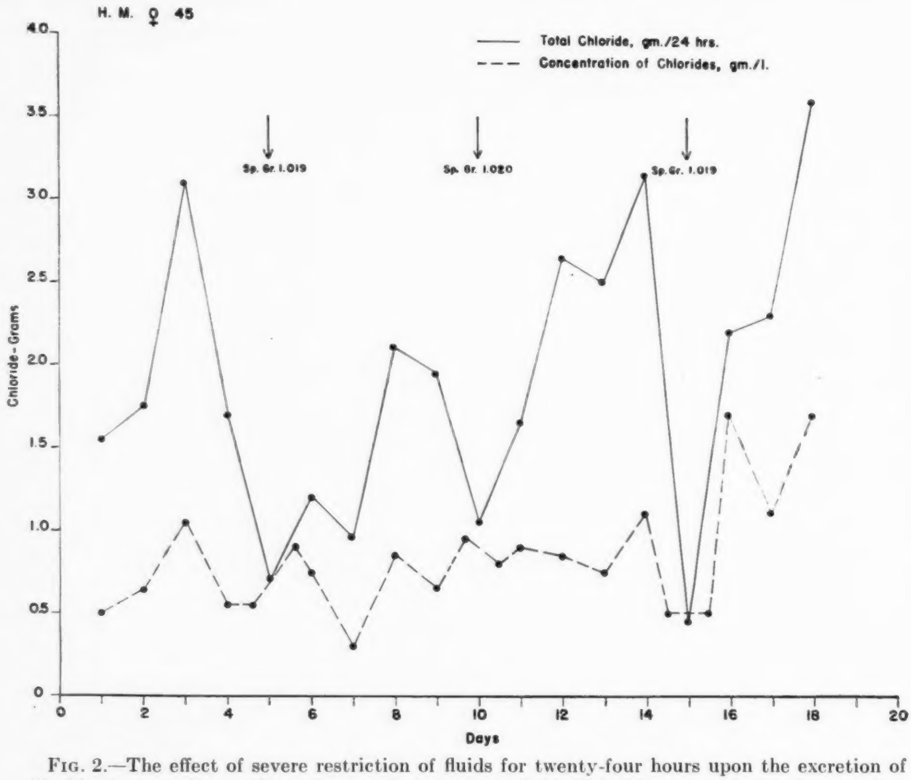


FIG. 2.—The effect of severe restriction of fluids for twenty-four hours upon the excretion of chlorides in a cardiac patient who was losing edema fluid. Chlorides are calculated as sodium chloride. The arrows at the top indicate the days on which the concentration test was performed. Although there were wide fluctations in the amount excreted, the concentration was relatively unaffected by the low urinary volume, indicating some relationship between volume and amount, and a deficiency in the ability of the kidneys to concentrate chloride.

Analysis of the data from a comparison of the change in weight expected from the removal of the fluid, and the actual loss of weight the day after it was removed, revealed discrepancies. In nine instances the calculated weight loss was greater by 0.5 Kg. or more than that which actually occurred, suggesting that fluid subsequently ingested was retained. In ten it

observation was thirty-one days. In most cases, diuretics were given; in others, fluids were removed mechanically (thoracentesis, paracentesis abdominalis, direct removal of edema by Southey tubes); in the remainder, no changes in therapy were made. While the Volhard-Arnold method for measurement of urinary chlorides is accurate at relatively high concen-

TABLE 4.—*Chloride and Protein Content of Abdominal, Pleural, and Edema Fluid*

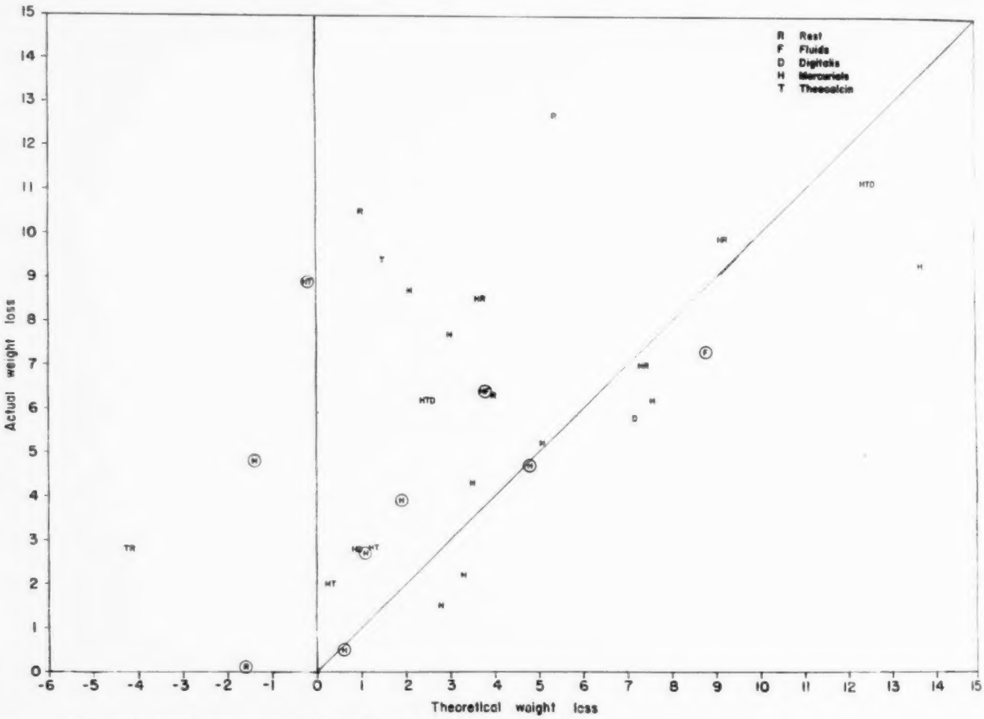
Case No. Date	Source of Fluid	Volume	Specific Gravity	Chlorides as NaCl Total	Chlorides as NaCl	Total Proteins	Weight Lost		
							Actual	Calculated	Difference**
		cc.		*Gm.*	*m. eq./L.*	*Gm./L.*	*Kg.*	*Kg.*	*Kg.*
20. W. H. ♂									
11/29/38	Abd.	10600	1.020	65.72	106.0	36.72	9.7	10.8	+1.1
12/12/38	Abd.	5200	1.017	31.6	104.3		4.8	5.3	+.5
21. E. H. ♀									
6/11/38	Pleura	1500	1.012	10.53	120.0		1.4	1.5	+.1
6/14/38		1500	1.010	10.31	117.4		1.4	1.5	+.1
6/24/38		1200	1.011	6.94	98.8		1.1	1.2	+.1
31. A. S. ♂									
10/12/38	Pleura	1600	1.010	10.67	112.8		2.5	1.6	−.9
27. F. M. ♀									
12/30/37	Edema	5300	1.011	39.11	126.2		7.3	5.7	−1.6
12/31/37		250	1.008	3.45	117.9				
16. H. M. ♀									
1/12/38	Pleura	850	1.016	5.85	117.6		1.5	.9	−.6
9/19/38		1150	1.017	6.50	96.6		1.3	1.2	−.1
9/23/38		1050	1.015	5.40	87.9		0	1.1	+1.1
8. B. H. ♂									
1/10/39	Abd.	15080	1.013	128.2	145.3	23.04	14.4	15.3	+.8
2/ 9/39		13000		74.1	97.4	23.6	13.6	13.0	−.6
3/16/39		8566		39.7	78.6*	27.2	8.9	8.7	−.2
6/26/39		9575	1.012	54.6	97.4†	28.8	—	9.6	—
9/ 5/39		14620	1.011	107.5	125.6	23.4	14.4	14.8	+.4
10/ 2/39		12440		65.9	90.6	27.2	13.1	12.4	−.9
43.§ J. P. ♂									
9/ 9/39	Abd.	6830		21.4	95.7	16.56			
24. E. C. ♀									
1/ 4/41	Pleura	1000	1.014	5.64	96.4	9.72	1.5	1.0	−.5
1/10/41	Edema	925	1.010	4.90	90.6 (L)		1.7	1.4	−.3
		495	1.010	2.57	88.8 (R)				
1/11/41		717	1.010	3.80	90.6 (L)		1.7	.9	−.6
		245	1.010	1.27	88.8 (R)				
1/12/41		214	1.010	1.13	90.6 (L)		.3	.2	−.1
		42	1.010	0.22	90.6 (R)				
1/28/41		1018	1.010	4.95	83.1		.7	1.01	+.3
1/29/41		1114	1.010	5.19	79.6		.5	1.1	+.6
1/30/41		1037	1.010	4.73	77.9		.3	1.0	+.7
34. J. Sc. ♂									
10/ 1/39	Pleura	2200		12.54	97.4	13.68	1.5	2.2	+.7
		1060		10.55	97.4	15.12	1.7	1.1	−.6
42§ A. G. ♂									
11/ 4/37	Pleura	1620	1.018	9.28	99.1		2.5	1.6	−.9

* Plasma Cl. 73.5 meq./L.
† Plasma Cl. 92.4 meq./L.
(L) Left leg.
(R) Right leg.

§ Diagnoses: Case 42—A. G. ♂, age 58. Arteriosclerotic heart disease.
Case 43—J. P. ♂, age 37. Arteriosclerotic heart disease. auricular fibrillation.
Other diagnoses given in table 5.
** + = fluid retained; − = fluid lost.

trations, inaccuracies of as great as 20 per cent may be found when the concentration is below approximately 15 m. eq. per L.[9] The total chloride content of the urine may therefore represent an erroneous value when the daily excretion is low. This error, however, does not invalidate entirely the results, for measurements of urinary chlorides take into account only one of three routes by which chlorides can be excreted from the body.

When the difference between the intake of salt and the urinary excretion of chlorides calculated as sodium chloride was considered as a fluid containing 100 m. eq. per L. of sodium chloride, there sometimes appeared to be a relation between this amount and changes in body weight (fig. 3). For purposes of comparison, the theoretic weight of this fluid was calculated on the basis of 1 Kg. per L., neglecting urinary solutes. The weight of fluids removed mechanically was subtracted from the total change in body weight. In 12 cases there was fairly good agreement between the theoretic loss of weight (fluids) calculated from



Note: Circles indicate that the patient died during the observation.

FIG. 3.—A comparison between the actual loss of weight of 29 patients suffering from congestive heart failure and the theoretical loss of weight as calculated from the output of chlorides in the urine. This figure was derived from the assumption that the amount of chloride excreted represented a fluid containing 100 m. eq. per L. (which would therefore be comparable to edema fluid). Those cases on the right of the isometric line represent instances in which a larger amount of chloride was lost than its equivalent of water, i. e., a comparative hydration occurred during diuresis. Those cases on the left of the line represent instances in which less chloride was lost than its equivalent of water, i. e., water without sufficient salt had been stored prior to diuresis. Those cases on the negative side indicate instances in which there was actual retention of chlorides during diuresis, and suggest that considerable hydration had previously existed. The periods of study are shown in table 5. Weight is in Kg.

TABLE 5.—*The Urinary Excretion of Chlorides Related to Changes in Body Weight*

	Age	Intake		Days of Observation	Urinary output		Change in Body Weight		Wt. Fluid* Equiv. to Cl.	Cause† of Diuresis	Diagnosis‡	Remarks§
		NaCl	Fluids		Cl as NaCl		Av./day	Total				
					Total							
		Gm./24 hrs.	cc./24 hrs.		Gm.	Gm./24 hrs.	Gm.	Kg.	Kg.			
6. J. B. ♂	68	1.0	1500	35	121.04	3.46	−266	−9.3	−14.7	Hg.	A.H.D. Aur.fib.	
7. P. O. ♂	65	0.5	various	37	33.70	0.91	−231	−8.6	−2.6	Hg.	A.H.D. C.H.B.	
		1.4	various	35	55.20	1.58	−80	−2.8	−1.2	Hg. Th.		
8. B. H. ♂	65	0.5	1200	40	50.38	1.26	−139	−5.2	−5.1	Hg.	A.H.D. Aur.fib.	+164.18 Gm. in abd. fluid
9. H. P. ♂	47	1.0	1500	28	26.95	0.96	−318	−8.9	+0.2	Hg. Th.	A.H.D.	Retention of H_2O. Died
10. L. S. ♀	41	1.8	1500	26	69.60	2.67	−242	−6.3	−4.0	Rest.	R.H.D. Aur.fib.	
12. A. J. ♂	52	0.67	various	49	111.83	2.28	−228	−11.2	−13.5	Hg. Th. Dig.	R.H.D.	
13. I. Y. ♂	57	1.0	2400	25	30.62	1.22	−112	−2.8	−0.9	Hg. Dig.	A.H.D.	
14. J. H. ♂	58	1.0	2000	10	26.25	2.63	−150	−1.5	−2.8	Hg.	R.H.D. Aur.fib.	
16. H. M. ♀	45	1.0	1500	30	74.90	2.50	−193	−5.8	−7.2	Dig.	R.H.D. Aur.fib.	
17. R. L. ♀	69	1.0	various	47	100.65	2.14	−215	−9.9	−9.2	Hg. Rest.	A.H.D.	
18. E. K. ♂	64	2.0	1000	31	67.75	2.19	−338	−10.5	−1.0	Rest.	A.H.D.	
19. M. J. ♀	44	1.0	2000	12	56.55	4.71	−517	−6.2	−7.6	Hg.	H.H.D. Aur.fib.	
20. W. H. ♂	58	1.0	various	50	56.47	1.13	−56	−2.8	−1.1	Hg.	A.H.D.	Died
21. E. H. ♀	69	1.0	various	24	46.31	1.93	−267	−6.4	−3.8	Hg.	A.H.D.	
22. C. M. ♂	11	1.0	various	22	50.19	2.28	−214	−4.7	−4.8	Hg.	R.H.D. Aur.fib.	Died
24. E. C. ♀	51	1.0	various	32	49.40	1.54	−241	−7.7	−3.0	Hg.	R.H.D. Aur.fib.	Retention of H_2O. Died. Plasma Cl low
25. W. D. ♂	42	1.0	2000	35	56.88	1.63	−243	−8.5	−3.7	Hg. Rest.	R.H.D. Aur.fib.	
		1.0	2000	10	30.70	3.07	−430	−4.3	−3.5	Hg.		
		1.0	2000	21	64.29	3.06	−333	−7.0	−7.4	Hg. Rest.		
		1.0	1500	66	41.33	0.63	−42	−2.8	+4.2	Th. Rest.		Retention of H_2O. Plasma Cl and Na low
26. A. K. ♂	43	1.1	various	53	84.45	1.59	−240	−12.7	−4.4	Rest.	R.H.D. Aur.fib.	
27. F. M. ♀	20	1.0	1500	4	55.60	13.90	−183	−7.3	−8.8	Hg.	R.H.D. Aur.fib.	Died
28. M. S. ♀	34	1.0	1500	13	3.91	0.30	−8	−0.1	+1.6	Rest.	R.H.D. Aur.fib.	Retention of H_2O. Died
29. O. C. ♂	39	1.4	various	20	19.69	0.98	−240	−4.8	+1.4	Hg.	R.H.D. Aur.fib.	Retention of H_2O. Died
30. J. K. ♀	30	1.0	1500	26	29.39	1.13	−192	−0.5	−0.6	Hg.	R.H.D.	Retention of H_2O. Died
31. A. S. ♂	43	1.1	various	31	46.16	1.49	−126	−3.9	−1.9	Hg.	R.H.D. Aur.fib.	Retention of H_2O. Died—accident
32. J. V. ♀	62	1.0	2000	55	69.39	1.26	−113	−6.2	−2.5	Th. Dig. Hg.	A.H.D.	Plasma Cl low
33. A. M. ♂	58	1.0	various	38	37.57	0.96	−294	−11.2	+0.1	Dig.	A.H.D. Aur.fib. Obesity	Wt. loss also
34. J. Sc. ♂	73	1.5	1500	19	11.3	0.59	+10	+0.2	+0.3		A.H.D.	Retention of H_2O. Died
35. N. J. ♂	67	1.0	2500	25	34.10	1.36	−376	−9.4	−1.5	Th.	A.H.D.	Plasma Cl low
36. M. H. ♀	48	1.0	1500	20	39.56	1.88	−110	−2.2	−3.3	Hg.	R.H.D. Aur.fib.	
37. S. D. ♂	45	1.0	2000	60	62.99	1.49	−333	−2.0	−0.3	Hg. Th.	H.H.D.	

* This figure was calculated from the weight of a theoretical fluid containing 100 meq./L. of sodium chloride. It represents the theoretical weight loss estimated from the net loss of chloride in the urine.

† Hg. = mercurial diuretics used; Th. = theocalcin; Dig. = digitalis given.

‡ A. H. D. = arteriosclerotic heart disease; C. H. B. = complete heart block; R. H. D. = rheumatic heart disease; H. H. D. = hypertensive heart disease; Aur. Fib. = auricular fibrillation.

§ Retention of fluids in the sense that the difference between the intake and output of fluids was excessive, dilution of electrolytes occurred, urine volume decreased, and nitrogen in the blood rose. This sequence of events has been reported.[14]

urinary chloride losses, and the actual loss of weight (table 5). In 6 cases the agreement was less close, and in 11 there were wide divergencies.

Only one case (J. B.) was divergent from the expected relationship in a direction indicating that the theoretic loss (from chloride) was greater than the actual loss, i.e., that salt depletion had occurred to a large extent. A period was chosen during which this patient received a total of 11.0 cc. of mercurial diuretics intravenously, resulting in a large loss of chloride in his urine. Ten of the 12 cases in which there was good agreement had received smaller amounts of mercurial diuretics (fig. 3).

On the other hand, the 11 cases which diverged markedly from the expected relationship between actual and theoretic weight loss diverged in a direction suggesting that more water and less chloride was lost. In 4 subjects there was actually a "positive" chloride balance in spite of the loss of weight. If this method of analysis is accurate enough for the purpose, these findings indicate that considerable water unaccompanied by chloride had been previously retained, and was lost via the urine and other routes during the period of observation.

An attempt was made to correlate differences between the fluid intake and the average daily urinary volume with the daily, weekly, or monthly loss of weight. No agreement was seen. While there was some rough correlation during short periods of diuresis, over longer periods the urinary volume was found to be the least exact of any method for the estimation of loss of edema.

Discussion

It is becoming increasingly evident that congestive circulatory failure is associated with disturbances of the balances of water and salt which are initiated by a failing circulation and mediated by the kidneys. These disturbances can act through two mechanisms: a direct renal one and an extrarenal one, probably involving endocrine influences.[10] There is evidence for both hypotheses.

In congestive failure renal blood flow has been found considerably reduced, enough to account for diminished excretion of sodium and chloride.[5] The theory has therefore been advanced that the retention of salt and water is on the mechanical basis of a decrease in the volume of glomerular filtrate and a shunting of blood away from the kidneys, without excessive tubular reabsorption of salt. Other functions, however, such as the ability to excrete nitrogenous products and water, are not interfered with to the same extent. Since both salt and nitrogenous products are filtered at the same rate, differences in their retention must be attributed to specific alterations in their respective rates of tubular reabsorption. Urea is reabsorbed passively by diffusion, salt actively. Three types of disturbance in the normal relations between filtration and reabsorption of salt could cause retention: (1) lowering of filtration rate without change in the absolute rate of reabsorption; (2) lowering of filtration rate with increase in the absolute rate of reabsorption; and (3) maintenance of filtration rate with increase in the absolute rate of reabsorption. None of these alternatives apply to the normal state. As to the first, in arterial hypertension and chronic glomerulonephritis low filtration rates are frequently seen without clinical evidence of salt retention; in aged persons filtration rates may fall to half normal values without edema developing[11]; the upright position and exercise are accompanied by lower filtration rates.[12, 13] It would appear, therefore, that normally a fall in filtration is usually accompanied by decreased reabsorption of salt. The third possibility is untenable in the light of the experimental evidence found in cases of congestive failure. The second possibility must therefore be considered carefully.

It is obvious that a marked reduction in renal plasma flow associated with less reduction in glomerular filtration rate will produce the conditions necessary for a tendency to retain salt, provided that the renal tubules remain in a constant state as regards reabsorption. The experiments reported here, however, strongly suggest that the tubules have increased their rates of reabsorption for salt, but not for nitrogen. The 2 patients studied by Merrill,[5] who had not received a mercurial diuretic, excreted 0.04 per cent and 0.01 per cent of

filtered sodium at glomerular filtration rates of 60 and 91 ml. per minute, a circumstance incompatible with nitrogen equilibrium if applied to other functions of the kidney. Assuming the lowest values of glomerular filtration rate found by Merrill (approximately 50 ml. per min.), calculations can be made on the present findings which show that chloride reabsorption was markedly increased above that expected, excretion having been only 0.7 to 16 $\times$ 10^{-5} per cent of the amount filtered. During some twenty-four-hour periods, none was detectable in the urine, although nitrogen and water excretions were not abnormal, and adequate intake of salt was assured. These levels for chloride excretion are of similar magnitude to those found by Merrill for sodium. The paradoxical depression of chloride excretion after higher intakes of salt seen in 6 of 9 patients suggests an extrarenal influence working to decrease filtration or to increase reabsorption of chloride. That this extrarenal influence did not affect filtration is indicated by the absence of depression of the clearance of urea when large amounts of salt were injected intravenously (fig. 1). In fact, we have seen the clearance of urea at twice normal values, while the ability to excrete salt was markedly impaired. A tendency to the formation of edema from hypoproteinemia was not accompanied by diminished excretion of salt (fig. 1).

Therefore, it becomes evident that the kidneys of cardiac patients exhibit a more marked depression of their ability to excrete salt than can be assumed from a lowered glomerular filtration rate. The salt-excreting function, which in normal subjects fails when the concentration in the urine is approximately 18.0 Gm. per L., appears in cardiac patients to break down at about 10 per cent of that value, or less. Such a low level, if applied to other excretory functions, is incompatible with normal nitrogen balance.

For one function of the kidneys to be altered and not others points to the action of extrarenal influences. The hormones of the adrenal cortex which regulate salt balance come to mind. If failure of the circulation in some way acts upon the adrenal cortex to stimulate the production of salt-retaining hormones, some of the findings would be explained. Deficient flow of blood through the kidneys, caused by a failing circulation and/or intrarenal circulatory alterations, would explain the remainder. The low concentration of sodium in sweat found in chronic congestive failure[10] is in accord with the hypothesis that the adrenal cortex is overactive.

There also appears to be a disturbance of water balance in many patients which is not wholly dependent upon a specific retention of salt. A considerable number apparently had retained more water than would be indicated by an isosmolar amount of salt in edema fluid. Unfortunately, adequate studies of the levels of sodium in plasma were not usually made, but there is enough evidence to suggest that dilution of electrolytes from the storage of water occurred in many of the more severely ill patients. Serum sodium and chloride levels were usually slightly lower than normal, indicating hemodilution; chloride levels in extracellular fluids were often considerably depressed. Diuresis in many was not accompanied by an amount of chloride sufficient to explain the loss of weight as occurring from the excretion of an edema fluid containing normal concentrations of salt.

While retention of water by the kidneys can be caused by renal failure alone, extrarenal factors probably exert greater effects than renal ones. The secretion of the posterior lobe of the pituitary and other antidiuretic substances may act as accessory influences, for kidneys must be very severely damaged to be unable to excrete water. One condition, the "low-salt syndrome,"[14] is recognizable, however, which depends upon disturbances of salt balance during which water is not excreted; this situation can sometimes be reversed by raising the levels of sodium and chloride in the body to normal. Whether or not antidiuretic hormones are at work in this condition is not known.

These studies suggest indirectly that there is excessive reabsorption of chloride, and probably sodium, by the renal tubules of patients in congestive failure. Other experiments have demonstrated a specific depression of the excretion of both sodium and chloride even under added loads. Calculations of the ratios of the clearances of inulin and chloride (C_I/C_{Cl})

under conditions of salt-loading reveal that in cardiac patients the ratio rises sometimes to twice normal values, assuming a glomerular filtration rate of 50 ml. per minute for cardiac and 100 ml. per minute for normal subjects.[4] For this ratio to remain at normal levels would require filtration rates of approximately 11 to 30 ml. per minute, which are very much lower than those found. Therefore, tubular reabsorption of salt must be increased. If this is so, the renal tubular work involved, judging from the calculations of Newburgh,[15] must be very large. The retention of 90 to 96 per cent of ingested or injected salt at adequate volumes of urine indicates the excessive work performed. It is difficult to ascribe this increase in renal work to insufficient oxygen in the kidneys; a more likely explanation is found in extrarenal factors stimulating renal tubules.

The mechanism of congestive circulatory failure therefore can be postulated theoretically according to the following: (1) The heart, by reason of myocardial failure or obstruction to filling, cannot meet the loads imposed by the requirements of the peripheral circulation and pumps less blood than is needed to supply the body with oxygen. It is not the purpose of this discussion to examine whether "forward" or "backward" failure predominates, nor is this question pertinent to the subject at hand. Inadequate flow of blood through the heart appears to be the initial stimulus. (2) Renal blood flow becomes reduced in response to some unknown stimulus, leading to a tendency to retain salt, water, and nitrogen. (3) A compensatory mechanism, probably involving the adrenal cortex and possibly anti-diuretic substances, is called into play, acting upon the principal fluid-regulating organs of the body, the kidneys. (4) Salt and water are retained by the kidneys through the action of salt and water-retaining hormones on the renal tubules. (5) The net result is an increase in blood volume and extracellular fluids, which may be an attempt to maintain homeostasis, but results in distress.

The control of the distress resulting from the accumulation of edema fluid, aside from the use of diuretic agents, involves the following measures: (1) Dietary restriction of sodium chloride to a level commensurate with the ability of the kidneys to excrete salt. This point has been repeatedly demonstrated and needs no discussion other than to emphasize that restriction of the intake of salt must often be rigid. (2) The volume of urine must be adequately maintained[15] which usually means an adequate or unrestricted intake of fluids. Excessively high fluids, however, in severely ill cardiac patients may result in excessive hydration and renal insufficiency. It may become necessary to measure, therefore, the levels of plasma sodium, chloride and carbon dioxide combining power in order to detect hydration, and in some cases to restrict fluids moderately. We have been unable to substantiate a recent report[16] which indicated that diets containing 3.0 Gm. of salt and restricted fluids were preferable to those with less salt and more fluids; in fact, all of our results point to the opposite as being true. (3) Severe depletion by diuretic agents of sodium and chlorides in body fluids must be avoided. (4) It is possible to prevent congestive failure from occurring, even when the potentialities for its development are present, by restriction of salt in the diet. The effects of diuretic agents will be discussed in a subsequent communication.

Summary and Conclusions

1. Fifty patients, of whom 39 suffered from congestive circulatory failure of cardiac origin, were studied. Urinary chlorides, water, and body weight were measured daily for long periods while the intake of salt and water was maintained at constant, but different levels.

2. The amount of chlorides excreted in the urine was either depressed, or was raised only slightly, when the intake of salt was increased, either by ingestion or by intravenous injection. Depression of nitrogen excretion did not accompany this alteration. The cardiac patient can excrete very little chloride under normal circumstances.

3. Restriction of the fluid intake usually resulted in retention of chlorides; elevation of the fluid intake sometimes initiated slight or moderate chloride diuresis.

4. A comparison of the theoretic loss of weight during recovery from failure calculated from the urinary excretion of chlorides, and the

actual loss, indicated that over one-third of the subjects were in a state of excessive hydration while in failure.

5. Congestive circulatory failure of cardiac origin is a disturbance of fluid balance initiated by the heart, but mediated principally through the kidneys. Disturbances of both salt and water balances can be present, which may be the result of hormonal effects upon renal regulatory mechanisms.

Acknowledgments

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Tracer Studies of the Urinary Excretion of Radioactive Mercury following Oral Administration of a Mercurial Diuretic

By William J. Overman, M.D., William H. Gordon, Jr., M.D., and G. E. Burch, M.D.

This report presents experimental evidence of the inefficient intestinal absorption of mercury following the oral administration of a mercurial diuretic. Radiotracer technic was employed using a diuretic prepared with radioactive mercury. Both control subjects and subjects with congestive heart failure were shown to absorb only a small percentage of the mercury administered by the oral route.

REPORTS on the efficacy of oral mercurial diuretics in control of edema in patients with chronic congestive failure have been in general agreement.[1–11] Employing the ability to control edema as a clinical index, various workers [1, 3, 4, 7] have found the preparations used to be effective in from 58 to 77 per cent of trials. The validity of this index, however, is questionable. The efficacy of a mercurial diuretic may also be evaluated from a knowledge of the absorption, blood concentration, and urinary excretion of mercury, the active agent common to this whole class of compounds[12]. Opportunities were available during the course of other studies to make these observations by tracing radiomercury chemically incorporated into a mercurial diuretic prepared for oral use. The tracer method permitted quantitative assay of many samples during each experiment.

Materials and Methods

The labeled mercurial diuretic "Mercuhydrin"* was prepared with radioactive mercury ($Hg^{203, 205}$)† such that each capsule of 0.33 Gm. contained approximately 60 mg. of "Mercuhydrin" (19.5 mg. mercury and 24 mg. theophylline), with lactose as a vehicle. The preparation was placed in plain or enteric-coated (shellac or salol) gelatin capsules. Each capsule was equivalent in mercurial content to 0.5 cc. of the parenteral preparation.

The specific activity of the capsules, as estimated by means of a mica window Geiger-Müller counter and a special mold, varied considerably, owing to individual variations in degree of filling. The activity of five *intact* capsules was compared with the activity of the *content* of each of these capsules dissolved in water and measured under conditions employed for the biologic preparations. A high correlation was found between the activity of the intact and dissolved capsules, the maximum deviation from the mean being 10 per cent (fig. 1). Thus, calculations of dosage in terms of radiomercury were possible.

Twenty-two control subjects and 5 subjects with chronic congestive heart failure were selected for study from the medical wards of the Charity Hospital (table 1). The control subjects were apparently free from any cardiovascular, renal, or metabolic disease; the majority had either recovered from an acute respiratory infection or were suffering from a chronic pulmonary disease. Only one subject had ever received a mercurial diuretic; this was a subject with chronic congestive heart failure and edema but he had not received any for two weeks prior to study. Additional therapy for the subjects in his group consisted of restriction of salt, digitalis, bed rest and sedation.

Of the 22 control subjects, 14 received the radioactive mercurial diuretic in plain gelatin capsules, 4 in capsules enteric-coated with shellac, and 4 in capsules enteric-coated with salol. All of the 5 subjects with congestive heart failure received the labeled diuretic in plain gelatin capsules.* The diuretic was administered as a single dose after twelve hours of fasting. Food and liquids were withheld for at least two hours after administration except for water needed to swallow the capsules. The dose for 23 sub-

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* The sodium salt of methoxyoximercuripropylsuccinylurea with theophylline, prepared with radiomercury in this laboratory by Messrs. Harold Krahnke, Darwin Kaestner, and Edwin Sprengler through the courtesy of Dr. H. L. Daiell, Director of Research, Lakeside Laboratories, Milwaukee.

† Radioactive mercury ($Hg^{203, 205}$) was obtained from the Isotopes Division of the Oak Ridge National Laboratories.

*One hundred mg. ascorbic acid was added to each capsule given to 5 of the control subjects who received the drug in plain gelatin capsules.

jects was 4 capsules, equivalent to 2.0 cc. of the parenteral preparation or 78 mg. of mercury. This represented approximately 40,000,000 counts per minute (range: 37,246,000 to 43,649,000) or roughly 0.1 millicurie. In 4 subjects the dose was 10 capsules, equivalent to 5 cc. of the parenteral preparation, 195 mg. of mercury, or approximately 100,000,000 counts per minute (range: 98,726,000 to 119,943,000) or 0.25 millicurie.

Samples of blood were obtained from an antecubital vein at ten to fifteen minute intervals from the first subjects studied, at thirty minute intervals from others, and at hourly intervals later in the series. Specimens of urine were collected by catheter in some patients; in others the samples were voided, collections being made until there was no further radioactivity demonstrable. Fecal specimens were obtained from a number of subjects, but accurate

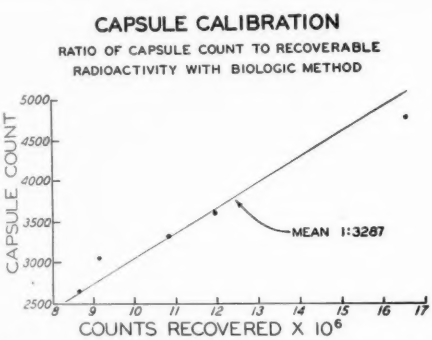

FIG. 1.—High correlation of counts obtained for 5 capsules selected at random and observed in the intact state and then with the counts of each dissolved in water by the use of the method for the biologic specimens. The points represent the values of each capsule and the line their mean.

quantitative determinations of their radiomercurial content were unsuccessful because of problems of self absorption and other difficulties peculiar to the handling of radiomercury.

RESULTS

Total urinary excretion of mercury following oral administration of the diuretic was low both in the control subjects and in the subjects with chronic congestive heart failure (table 1). Urinary recovery of the oral dose varied from 11.79 per cent to 0.00 per cent, with an average of 3.86 per cent. The largest percentage of recoveries was obtained after administration of the drug in plain gelatin capsules (table 1, A, B, and E), and the smallest recoveries occurred following its use in

TABLE 1.—*Summary of Results Obtained with Oral Mercuhydrin for All Subjects*

Subject	Age (yrs.)	Diagnosis	Urinary recovery (per cent)	Clearance time (min.)
A. Control subjects who received dose of 10 plain gelatin capsules				
E. H.	31	Convalescing pneumonia	3.60	1420
J. H.	14	Pleural effusion, clearing	8.90	1298
W. G.	29	No disease	4.23	1347
W. O.	29	No disease	6.60	1700
B. Control subjects who received dose of 4 plain gelatin capsules				
O. P.	32	Convalescing pneumonia	3.86	1410
F. M.	46	Tuberculous adenitis	4.33	1440
E. M.	28	Convalescing pneumonia	11.79	1350
L. W.	55	Convalescing pneumonia, anemia	0.72	1205
I. B.	54	Convalescing pneumonia	6.41	1630
E. D.	63	Severe nutritional anemia, corrected by transfusion	2.31	1765
S. C.	50	Bronchogenic carcinoma	4.03	1764
I. H.	68	Possible pernicious anemia, normal hemogram	7.07	1690
L. H.	19	Convalescing pulmonary abscess	4.57	837
E. P.	47	Bronchogenic carcinoma	5.53	1513
C. Control subjects who received dose of 4 shellac-coated capsules				
V. D.	29	Sterile synovitis	0.23	325
Jo. H.	31	Pulmonary abscess	0.04	156
J. M.	55	Bronchogenic carcinoma	0.00	0
L. P.	15	Bronchiectasis, afebrile	0.00	0
D. Control subjects who received dose of 4 salol-coated capsules				
A. B.	29	Tuberculous adenitis	1.19	1035
A. J.	20	Convalescing pneumonia	0.06	550
T. J.	44	Guillain-Barré syndrome	1.86	930
H. M.	51	Bronchiectasis, afebrile	2.55	1510
E. Subjects with congestive heart failure who received dose of 4 plain gelatin capsules				
R. C.	50	Hypertensive cardiovascular disease, failure	8.23	1365
L. M.	61	Arteriosclerotic heart disease, hypertensive cardiovascular disease, diabetes, failure	0.18	785
F. N.	50	Rheumatic heart disease, failure, chronic glomerulonephritis	9.40	5045
F. S.	68	Hypertensive cardiovascular disease, failure	3.12	1905
R. W.	66	Syphilitic heart disease, failure	3.38	815

enteric-coated capsules (table 1, C and D). The addition of ascorbic acid to the diuretic in control subjects (last 5 subjects, table 1, B) did not appreciably affect urinary excretion of mercury.

The shellac-coated capsules were extremely resistant to dissolution in the intestine; 50 per cent of those administered were recovered intact in the stools. Although the capsules coated with salol dissolved in the gastrointestinal tract, urinary excretion of mercury was essentially one-fourth of that observed following administration of the diuretic in plain gelatin capsules.

Three of the four control subjects who received a single dose of ten capsules experienced toxic reactions manifested by abdominal cramping and diarrhea. A dose of four capsules produced no toxic symptoms. There was no significant difference noted in percentage of mercury recovered in the urine of the groups receiving these two quantitatively different doses in plain gelatin capsules (table 1, A, B, and E).

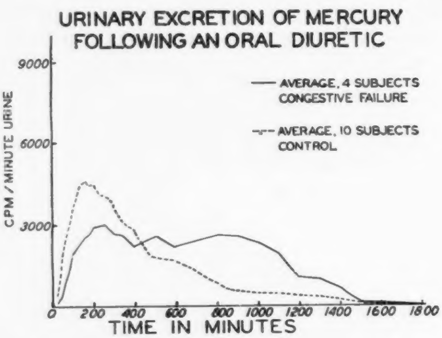

FIG. 2.—Comparison of the time course of the average rate of urinary excretion of mercury in 4 subjects with chronic congestive heart failure with that in 10 control subjects.

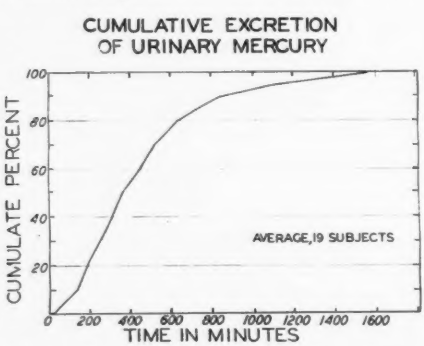

FIG. 3.—Cumulative urinary excretion of mercury for all subjects who received the diuretic in plain gelatin capsules, the 100 per cent value being based upon the total amount excreted in the urine.

The total urinary excretion of mercury following a dose of four plain gelatin capsules was similar both for the control subjects and for those with chronic congestive heart failure (table 1, B and E). The excretion rates were qualitatively different in that the maximum level of urinary concentration was lower and more prolonged for subjects with heart failure than for the control subjects (fig. 2).

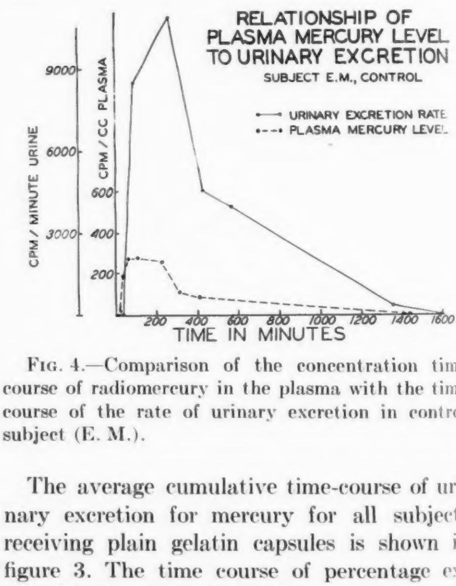

FIG. 4.—Comparison of the concentration time course of radiomercury in the plasma with the time course of the rate of urinary excretion in control subject (E. M.).

The average cumulative time-course of urinary excretion for mercury for all subjects receiving plain gelatin capsules is shown in figure 3. The time course of percentage excreted is based on the total amount recovered in the urine and not on the dose administered. Seventy per cent of the excreted mercury was found within 500 minutes (8.3 hours) after administration of the diuretic. The remainder was slowly excreted over an additional 1,090 minutes (16.2 hours). The average total time for urinary excretion was 1,590 minutes (26.5 hours), the extremes being 785 and 5,045 minutes (13 and 84.1 hours).

Maximum concentrations of radiomercury in the plasma coincided in time with the periods of maximum urinary excretion of the tracer

(figs. 4 and 5). In general, the plasma concentrations were low in comparison with equal doses administered intramuscularly and intravenously,[13] with one notable exception, a subject with congestive heart failure, chronic glomerulonephritis, and mild uremia (Subject F. N., table 1). The concentration of mercury in the plasma of this subject was higher and was maintained longer than in the other subjects (fig. 5), the tracer being detectable in the urine over a period three times as long as that of the average, 5,045 minutes or 84.1 hours.

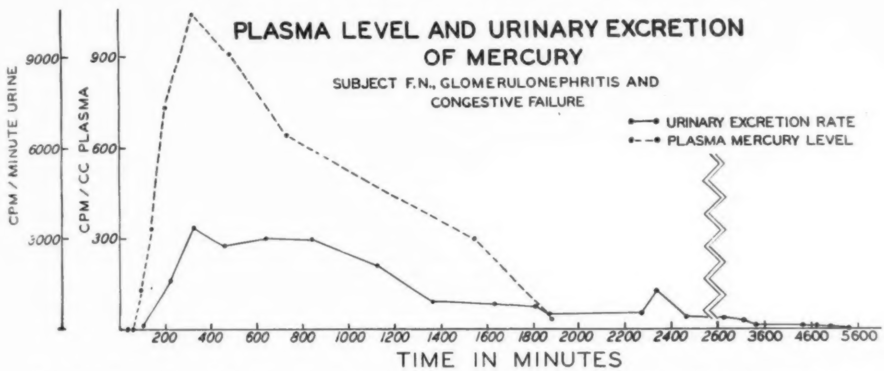

FIG. 5.—Comparison of the concentration time course of radiomercury in the plasma and the time course of the rate of urinary excretion in Subject F. N., who had chronic congestive heart failure and chronic glomerulonephritis.

Discussion

Even though the radiomercurial content of the stools could not be accurately quantitated, it was possible to demonstrate the presence of large amounts of mercury in specimens passed in the interval from 240 to 4000 minutes (4 to 66.6 hours) following administration. The large quantities passed in the stools indicate that if there is bodily retention or storage of mercury following oral administration, it is small.

The relatively long duration of detectable levels of radiomercury in the plasma of a patient with impaired renal function who excreted small quantities of mercury in the urine over an extended period of time (fig. 5) suggests that most of the mercury entering the blood stream is eliminated through the kidneys. Evidence supporting such a concept is offered by the close correlation between blood level and rate of urinary excretion observed for all subjects and is illustrated for 2 of these in figures 4 and 5. This would indicate that most or practically all the mercury found in the stool passed through the gastrointestinal tract unabsorbed rather than having been absorbed and then re-excreted into the bowel. Repeated experiments in this laboratory with the labeled diuretic administered parenterally[13] confirm this opinion. The possibility of an enterohepatic cycle is ignored.

Regardless of the mechanism or mechanisms involved, only small amounts of the radiomercury are recovered in the urine after oral administration of the diuretic. Since the diuretic effect of mercury is dependent to a large extent, if not entirely, upon its action on renal tubules,[12] it would appear that only that mercury which finds its way into the kidney produces diuresis. The degree of diuresis has been reported to be proportional to the amount of mercury excreted in the urine.[14, 15]

For each of a series of two widely different dosages an average of 5.0 per cent of the mercury administered found its way into the urine.[14, 15] Theoretically it is possible to administer an oral dose sufficiently large so that 5.0 per cent of it would produce diuresis. Approximately 60 per cent* of the mercury of a comparable mercurial diuretic (Salyrgan) admin-

* Unpublished data from this laboratory indicate this figure is much higher with Mercuhydrin.

istered intravenously is recoverable in the urine.[14, 16] Therefore, to produce the equivalent urinary excretion of 1.0 cc. of an intravenously administered dose it would be necessary to administer orally an equivalent of 12 cc. or 24 capsules. However, a dosage of 10 capsules was found to produce gastrointestinal irritation in 3 out of 4 control subjects. Multiple doses may solve the problem, but they may still cause gastrointestinal disturbances without resulting in sufficient urinary excretion to produce diuresis, since some mercury remains in the gastrointestinal tract for several days after administration. A patient with renal damage and a prolonged period of urinary excretion for mercury, such as Subject F. N. (table 1 and fig. 5), might accumulate enough mercury following repeated oral administration to achieve diuresis provided mercurialism does not supervene following repeated doses.[3, 6]

The poor urinary excretion following the use of the salol-coated preparation indicates that when mercury is available, maximum absorption occurs relatively high in the gastrointestinal tract (stomach or duodenum), at a level higher than that at which dissolution of salol occurs.

Summary and Conclusions

By means of tracer methods the absorption, blood concentration and urinary excretion of mercury following oral administration of standardized single doses of plain and enteric-coated capsules of a mercurial diuretic were studied in 22 control subjects and in 5 subjects with chronic congestive heart failure.

Enteric coating of the capsules resulted in the lowest blood concentrations and in the poorest urinary excretion of mercury, which indicates that maximum absorption occurred high in the gastrointestinal tract. Even with the more efficient plain gelatin capsules the blood concentration was low compared with intravenous administration, and the amount excreted in the urine averaged only 5.0 per cent of the amount administered orally. The addition of ascorbic acid had no significant influence on urinary excretion. In no instance did oral administration of the diuretic result in a urinary excretion of mercury equivalent in amount to that following a therapeutic parenteral dose, even though the drug was administered orally in toxic doses to several subjects.

In one subject with chronic glomerulonephritis prolonged retention of mercury was demonstrated, indicating the possibility of toxicity from repeated doses in patients with this disease.

The observations of poor absorption, low blood concentration, and low urinary excretion of mercury following oral administration of this mercurial diuretic precludes its general use in the treatment of chronic congestive heart failure.

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Experience with Thiomerin, A New Mercurial Diuretic

By Harold J. Stewart, M.D., Herbert I. McCoy, M.D., Edward M. Shepard, M.D., and E. Hugh Luckey, M.D.

Thiomerin, a new mercurial diuretic, was given subcutaneously to 109 patients in whom fluid accumulations were present. Most patients suffered from congestive heart failure. It was used first under close supervision in hospitalized patients and later in ambulatory patients. In certain patients it was possible to compare the diuretic response to Thiomerin given subcutaneously with that to Mercuzanthin and/or Mercuhydrin given intramuscularly or intravenously. The untoward effects of these mercurial diuretics were compared with those caused by Thiomerin. The advantages of a subcutaneous mercurial diuretic are pointed out.

SINCE the introduction of Salyrgan by Bernheim[1] in 1924, a continued search has been made for potent, more easily administered, less toxic mercurial diuretics Salyrgan and Novasurol could be given only intravenously because of local tissue damage if any escaped from the vein. It was later observed that the inclusion of theophylline in the solution to be injected not only enhanced the diuretic effect of the mercurial radical, but also markedly diminished the deleterious tissue reaction which occurred if any of the drug escaped into the subcutaneous tissues. As a result, certain preparations incorporating this principle were made. It was found that these drugs could be given intramuscularly without tissue damage.

In the continued search for less toxic drugs in this category of diuretics, a new mercurial diuretic, Thiomerin, was recently introduced. It was found by early tests that it was an effective diuretic when given intravenously and intramuscularly, but, more important, that it could be given subcutaneously without local tissue damage and with satisfactory diuresis. Thiomerin differs from the mercurial diuretics which preceded it in that it is a mercaptide. Moreover it is not combined with a xanthine drug as are both Mercuzanthin* and Mercuhydrin.† It is the disodium salt of N-(gamma-carboxymethylmercaptomercuri - beta - methoxy)-propyl camphoramic acid and has the following structure:

$C(CH_3)_2C(COONa)(CH_3)CH_2CH_2CHCONHCH_2CH(OCH_3)CH_2HgSCH_2COONa$.

Dissolved at a pH of 7.5, it contains approximately 0.039 Gm. of mercury per cubic centimeter, as do Mercuzanthin and Mercuhydrin.

Lehman,[2] in a comparative study of the cardiac toxicity of the mercurial diuretics, found that the intravenous administration of Thiomerin to anesthetized cats caused no immediate changes in the electrocardiogram in doses up to 160 times the maximal tolerated dose of Mercuhydrin and up to 225 times that of Mercuzanthin. Taube, Lehman and King[3] found that the intramuscular injections in rats of each of the three drugs, Thiomerin, Mercuhydrin and Mercuzanthin, caused an initial inflammatory reaction and exudate. Microscopic changes thought to be irreversible were present 96 hours following the injection of both Mercuhydrin and Mercuzanthin, but the exudate was completely reabsorbed in those animals receiving Thiomerin.

Grossman, Weston, Edelman and Leiter,[4] in a preliminary report of the results of administration of approximately 200 subcutaneous injections of Thiomerin, found the diuretic effect to be similar to that following Mercuzanthin and Mercuhydrin. Herrmann, Chriss, Hejtmancik and Sims[5] present evidence that Thiomerin has the following advantages over the older organic mercurial diuretics: it is less toxic; it can be given subcutaneously and has a more even diuretic action. Recently Batterman, Unterman and DeGraff[6] have reported observa-

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* Campbell Products Inc., New York, N. Y.

† Lakeside Laboratories, Cleveland, Ohio.

tions on the use of Thiomerin which also indicate that it is an effective diuretic agent.

The effects of Thiomerin* have been observed on the pavilions and in the out-patient Cardiac Clinic of the New York Hospital in 109 patients during the last fourteen months.

Methods

Patients who were selected for this study had evidence of accumulation of excess fluid in the tissues. Most of the patients were suffering from congestive heart failure. Fifty-two patients were treated in the pavilions of the New York Hospital. Most of them were at rest in bed. The salt in the food was limited to 1.0 to 3.0 Gm. daily. Fluid intake was restricted in certain patients to 1000 to 1800 cc. daily and in others it was not limited. Whenever possible the patient was weighed daily and the twenty-four-hour fluid intake and urine output were recorded. Thiomerin was substituted for Mercuzanthin or Mercuhydrin in patients who had been receiving these drugs in order to form the basis for comparisons. In others, Thiomerin was used as the initial diuretic and an occasional injection of Mercuzanthin or Mercuhydrin was given to observe their effects by way of comparison. The dosage of Thiomerin varied from 0.25 cc. to 2.0 cc. The amount and frequency of administration were governed by the patient's requirements.

The drug was given subcutaneously in nonedematous areas to all patients but two. To one of these it was given intravenously because of the appearance of moderately tender local nodules at the site of the subcutaneous injections. To the other one it was given intravenously because of extreme emaciation. One patient was taught to give herself the injections subcutaneously. This practice has continued satisfactorily to the present.

Fifty-seven ambulatory patients were treated in the Cardiac Out-Patient Clinic of the New York Hospital. The regimen was similar to that followed for the pavilion patients except that measurement of the daily urinary output was not recorded. Weight records were kept, however.

Observations

Thiomerin was given to 109 patients, 52 being pavilion and 57 ambulatory patients. Twelve of the pavilion patients also received the drug in the Cardiac Clinic. Five of the 57 ambulatory patients are not included in the statistical analysis as they received single injections and follow-up data were not available. There were no immediate untoward reactions following these single injections. Fifty-seven of the patients were males and 47 females. The ages ranged from 14 to 86 years.

Ninety-four patients presented evidence of congestive failure. The etiology of the heart disease was rheumatic fever in 26, arteriosclerosis in 26, hypertension in 12, both arteriosclerosis and hypertension in 21, constrictive pericarditis (postoperative) in 5, syphilis in 3, pulmonary fibrosis in one and a congenital anomaly in one. Nine other patients were treated because of evidence of excess fluid in the tissues. In 5 of these the diagnosis was cirrhosis of the liver, in 2 hepatitis, and in 2 carcinomatosis.

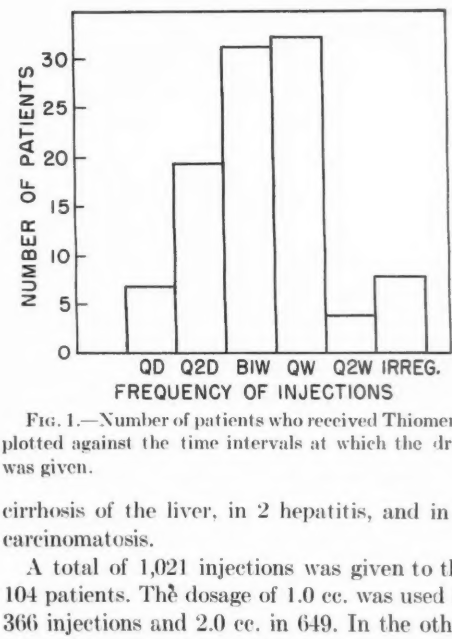

Fig. 1.—Number of patients who received Thiomerin plotted against the time intervals at which the drug was given.

A total of 1,021 injections was given to the 104 patients. The dosage of 1.0 cc. was used in 366 injections and 2.0 cc. in 649. In the other six injections, intermediate amounts were given. The initial dose was usually 1.0 cc. Smaller doses than this were given when sensitivity to mercury was suspected. In one patient, 1.0 cc. proved to be too large and 0.5 cc. was given subsequently.

The frequency of injections is recorded on figure 1. Most patients received injections on a bi-weekly or weekly schedule. In 9 patients, daily injections were given, although this is not usually recommended. On the daily schedule, however, few received more than six injections.

* Thiomerin was supplied by Campbell Products Inc., New York, N. Y.

One individual was given 2.0 cc. of the drug daily for sixteen days, without experiencing untoward effects. Excellent diuresis resulted in a weight loss of 9.0 Kg. The largest number of patients received from six to ten Thiomerin injections; 5 received more than thirty-one, and 2 more than fifty.

The diuretic effect of Thiomerin in a 78 year old man suffering from congestive failure is shown in figure 2. Dyspnea, orthopnea, pulmonary edema and massive anasarca were present. He was digitalized on admission and placed on a 3.0 Gm. salt diet. Nine injections of Thiomerin were given over a twenty-one-day period. Excellent diuresis resulted in a weight loss of 16.0 Kg. Because of the patient's difficulty in voiding, an indwelling catheter was maintained in place during the period of these observations. The collection and measurement of urinary output were therefore accurate.

The diuretic effect of Thiomerin was compared with that of Mercuzanthin in similar dosages in 54 patients and with that of Mercuhydrin in 22, regarding loss in weight or diuresis or both. In 5 patients the latter was possible. One significant difference between Thiomerin and the other two drugs was observed in 67 of these patients. Thiomerin resulted in a more even and more prolonged diuresis, which usually began twelve to eighteen hours after the injection and might continue for forty-eight hours. In 11 patients, Thiomerin was superior to either of the older mercurials. Five of these patients had received Mercuhydrin before Thiomerin was given, 5 Mercuzanthin and one had been given both drugs. Its superiority was manifested by more marked diuresis with greater loss of weight and by subsequent clinical improvement. As a result, Thiomerin could be given to these patients either less frequently or in smaller amounts than had been possible with the other mercurial drugs.

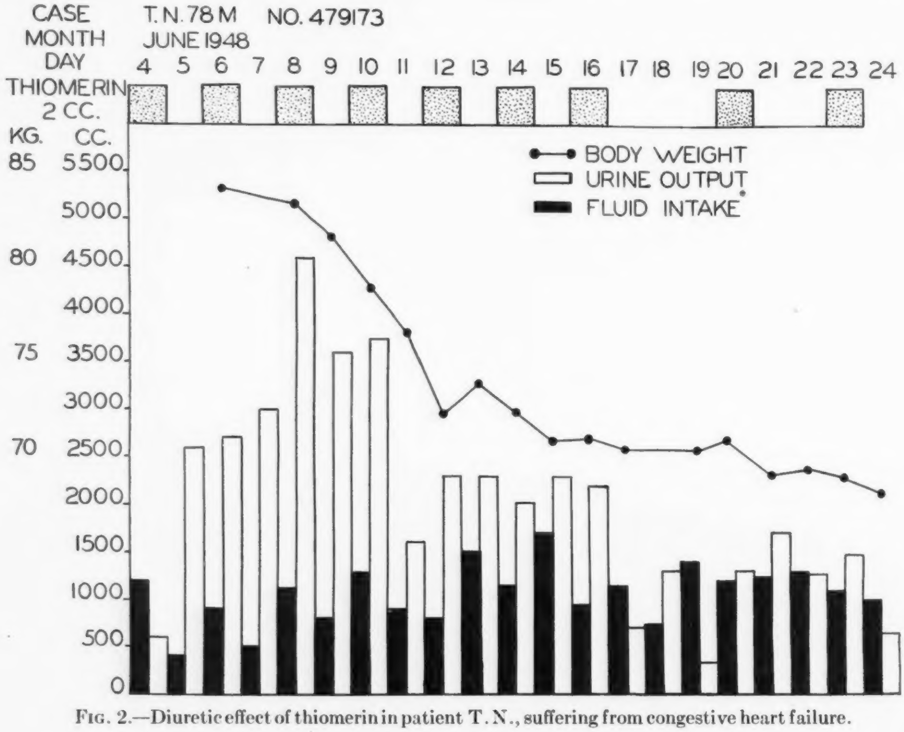

FIG. 2.—Diuretic effect of thiomerin in patient T. N., suffering from congestive heart failure.

Thiomerin was substituted for Mercuzanthin and Mercuhydrin in 3 patients because of sensi-

tivity reactions to these drugs. In one of these 3 patients a rash and fever followed on each occasion that Mercuhydrin was given. Mercuzanthin in 2.0 cc. amounts given intravenously had become relatively ineffectual. The patient suffered from severe congestive failure and massive anasarca was present. One cubic centimeter of Thiomerin was given subcutaneously on six occasions over a seven-day period. Diuresis was marked, resulting in a weight loss of 9.9 Kg. Five more injections over a ten-day period resulted in a further loss of 6.6 Kg. in weight with dramatic clinical improvement. Untoward reactions to Thiomerin have not appeared in this patient. Since then, she has received more than fifty injections in the Cardiac Clinic. The second patient developed an urticarial reaction to Mercuhydrin and the third, the same type of reaction to Mercuzanthin. Thiomerin has been effective as a diuretic in both of these patients without sensitivity reaction.

The diuretic effect of Thiomerin did not seem inferior to the effects of the other mercurial drug to which it was compared in any patient. In 22 patients an opportunity for comparison with the other mercurial drugs was not possible as only a few injections of Thiomerin were required to effect adequate diuresis, after which diuretics were no longer required.

Two patients received the drug intravenously subsequent to its use by the subcutaneous route. In them the total diuretic effect was approximately the same as by the subcutaneous route, although the onset of diuresis was more rapid and its duration less prolonged.

An estimate of the effect of Thiomerin on the body weight was possible in 89 patients. Loss of weight occurred in 47. The weight remained stable in 41 subjects. Only one patient in the whole series gained weight due to fluid accumulation while receiving Thiomerin in adequate dosage and frequency. This subject was a 44 year old alcoholic suffering from cirrhosis of the liver. Ascites was increasing. No better effect resulted from Mercuhydrin than from Thiomerin in similar amounts.

Eighty-six patients were on maintenance amounts of digitalis; 26 were also receiving ammonium chloride. In 7 patients when ammonium chloride was discontinued temporarily, slight but definite decreases in diuresis and gains in weight were recorded.

Reactions to Thiomerin

Temporary local pain or tenderness was the most common complaint. It occurred occasionally in 42 patients. The discomfort usually lasted from one minute to one hour and was described as varying from mild to moderate in intensity. In rare instances it was described as having a burning quality. Discomfort was accompanied in 4 patients by local ecchymosis which subsequently cleared entirely and did not prevent the continued use of the drug. In 6 other patients, moderately tender nodules appeared occasionally at the sites of injection. These were slowly reabsorbed over a seven- to ten-day period. In one patient they appeared more frequently and were more persistent. For this reason the drug was subsequently given by the intravenous route without untoward reaction. These reactions have not occurred with later batches of the drug.

Cramps in the calves of the legs were recorded in 3 patients when the diuresis was perhaps too large and too rapid. When either the dose of the drug or the frequency of injections was reduced these symptoms did not occur.

A superficial slough occurred in the skin in one patient. This untoward result followed the ninth injection the patient had received. It was given superficially and quite likely, in part, intradermally. The use of the drug was subsequently continued in this patient, with precautions taken for subcutaneous administration, and the area of superficial slough healed without further untoward reactions. This reaction was attributed to the drug being given too superficially.

Reactions were not observed in 58 patients.

Discussion

Our observations indicate that Thiomerin is as effective a diuretic agent as Mercuzanthin and Mercuhydrin. In a small number of patients in whom comparison was possible it appeared to be more effective than the latter two drugs so that smaller doses and less frequent injections

could be given. In no instance was it found to be inferior.

In addition, it has a major advantage over these two drugs in that it can be given subcutaneously. Thus, as experience with the drug accumulates, patients may be taught to administer this drug to themselves, just as they do with insulin. One patient of this group and two others not included because of incomplete data have been injecting the drug subcutaneously to themselves safely. A study is being set up with the idea of exploring the possibility of patients administering the drug themselves.

With few exceptions, patients, who have been receiving mercurial diuretics intramuscularly or intravenously, expressed preference for the subcutaneous route. In some patients much persuasion was required before they would submit to intermittent injections of the older mercurial drugs in order to obtain comparative observations.

Another advantage appreciated by most patients was the more even and persistent diuretic effect, sometimes lasting for several days. Many of the patients attending the afternoon Cardiac Clinic had become accustomed to little sleep on the night following injections because of profuse diuresis. When Thiomerin was substituted, certain patients remarked that less sleep was lost. With the use of this drug, also, complaints of cramps in the calves of the legs have become rare.

For the patient who was sensitive to Mercuhydrin and relatively refractory to Mercuzanthin, Thiomerin appeared to be life-saving. Diuresis resulted in a weight loss of 16.5 Kg. over a seventeen-day period. In 2 other patients who developed urticaria following the other mercurial diuretics, sensitivity to Thiomerin did not occur. Ammonium chloride appeared to enhance the action of Thiomerin.

There were no serious immediate or delayed toxic reactions to Thiomerin. Pain, palpitation, collapse, dyspnea, cardiac arrhythmias and evidences of renal damage were not observed. To one patient, injections of 2.0 cc. amounts of the drug were administered on sixteen consecutive days without toxic manifestations. This method of administration is, however, not recommended because of the danger of a cumulative effect of mercury and the untoward effects of extreme dehydration.

There is one drawback which the manufacturers are improving with each new batch of the drug. It cannot be made up in solution before distribution by the manufacturer because it is unstable. The latest batches which have been supplied to us may be kept without deterioration up to four to six weeks after being dissolved, provided they are kept in an icebox.

The results in these patients lead us to conclude that Thiomerin is a valuable contribution to the list of mercurial diuretic drugs. It appears to be as effective as the older ones and has the advantage that it can be given subcutaneously. Moreover, from animal experiments, it appears less toxic than these, but care must be exercised that it is given subcutaneously and not in the skin. At the present time it appears to be the diuretic of first choice.*

Summary

Thiomerin is a new mercurial diuretic which may be given subcutaneously as well as intramuscularly and intravenously. One hundred and nine patients with evidence of excess fluid in the tissues, most of them suffering from congestive heart failure, were given a total of 1,021 injections of the drug. From this experience we feel the drug is an effective diuretic agent. The local discomfort from the injection when it is given subcutaneously is minimal. In a few patients a subcutaneous nodule appeared at the site of injection in early preparations of the drug, but this reaction has not followed the later preparations of the diuretic. Care must be exercised that the drug is given subcutaneously and not intradermally.

Thiomerin was compared to Mercuzanthin or Mercuhydrin or both in 84 patients. In 67 of this group the total diuretic effect was similar in all three drugs. A more prolonged and more even diuresis, however, followed the use of Thiomerin. In 11 patients the total diuretic effect of Thiomerin was superior to these and

* Since this paper was accepted for publication, 2,315 additional subcutaneous injections of Thiomerin have been given over an eight month period. This further experience has increased our confidence in this drug as a diuretic agent.

the dose and frequency of injections could therefore be decreased. In 3 patients it was substituted because of sensitivity to Mercuzanthin or Mercuhydrin and was tolerated without sensitivity reaction. No serious toxic effects occurred. Thiomerin appears to us to be the drug of first choice at the present time for most patients requiring mercurial diuretics.

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Studies on Thiomerin—A Subcutaneously Administerable Mercurial Diuretic

By J. Grossman, M.D., R. E. Weston, M.D., Ph.D., I. S. Edelman, M.D., and L. Leiter, M.D., Ph.D.

Results of clinical and physiologic studies with Thiomerin, a new subcutaneously administered mercurial diuretic, are presented. The data indicate a clinical diuretic efficacy comparable to that of other mercurials and a negligible systemic toxicity. Renal clearance studies demonstrate that it acts by producing a reversible depression in tubular reabsorption of electrolyte and water. The effects of intravenous and subcutaneous administration are compared.

The role of organic mercurial diuretics in treatment of the edema of congestive heart failure and other conditions involving fluid retention is well established. However, because toxic manifestations, including fatalities, occur at times after the administration of these compounds,[1–3] less toxic mercurial diuretics have been sought. Lehman[4] found Thiomerin, the disodium salt of N-(γ-carboxymethylmercaptomercuri-β-methoxy)-propyl camphoramic acid, markedly less toxic than other organic mercurial diuretics, as measured by the intravenous dose required to produce electrocardiographic changes in cats. Subsequently, he observed that Thiomerin could be injected subcutaneously in animals without causing local tissue damage or evidence of pain.[5] Clinical trial of this potential, subcutaneously administerable diuretic was suggested, first, because Thiomerin is chemically identical with Mercuzanthin (sodium salt of β-methoxy-γ-hydroxymercuripropylamide of cyclopentane dicarboxylic acid theophylline) except for the substitution of a monothiol for the theophylline; and, second, because monothiols, unlike dithiols which inhibit diuresis, have been demonstrated to reduce the cardiotoxic effects of organic mercurials without affecting diuretic action.[6]

Material and Methods

The subjects were 21 hospitalized patients and 12 outpatients, most of whom were in well established chronic congestive cardiac failure of varying etiologies. Of these, the etiology was rheumatic fever in 11, hypertension in 7, coronary arteriosclerosis in 11, combined congenital anomaly and hypertension in one, and cor pulmonale in one patient. Two patients had localized edema; in one due to immobilization and in the other to an unknown cause. Despite the relatively advanced state of their illnesses, marked peripheral edema was uncommon, owing largely to a well controlled, low-sodium intake of less than 800 mg. daily.[7] Under this dietary regimen, the need for mercurial diuretics fell sharply.

In general, therapy other than mercurial diuretics was not influenced by our study. Digitalis and quinidine were given as indicated; ambulation was encouraged when the patient's condition permitted it. Ammonium chloride was not given since chloruresis was utilized as a measure of response. To limit the number of variables, adjuvant therapy such as aminophylline was avoided. Mercurials were administered in terms of the patients' needs and by the following routes: Thiomerin generally subcutaneously, Mercuzanthin intravenously, and Mercuhydrin (methoxyoximercuripropylsuccinyl urea) intramuscularly. The dosage of any mercurial never exceeded 2 cc., which is equivalent to 80.0 mg. of mercury; occasionally smaller amounts were used. More than three hundred injections have been given.

In the hospital, diuresis was followed by measuring the volume and chloride concentration of daily twenty-four hour urines. Daily urinary excretion of creatinine was not determined. However, the fairly constant daily chloride excretion on a fixed, low-salt intake indicates the accuracy of the urine collection. Patients were weighed daily on the same scale at about the same time of the morning. Because measurement of fluid intake is frequently unreliable on general hospital wards, these data are not reported. Patients from whom accurate collections could not be obtained were eliminated from the study.

Outpatients were instructed to return for reweighing at the same hour the day following an injection of a mercurial. Where this was not feasible,

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the patients were asked to weigh themselves on the same scale, at or near their homes on the day of, and the day after, the injection, wearing the same amount of clothing. In a few instances, these patients measured and reported their own twenty-four hour urine output.

In a smaller series of normal subjects and patients in congestive failure, the early effects of Thiomerin and Mercuzanthin on the renal clearances of mannitol, para-amino hippurate, sodium, chloride, and at times, uric acid were studied by the usual constant infusion technic of Smith and his associates as outlined by Goldring and Chasis.[8] Blood samples were collected by means of an indwelling needle placed in the femoral artery under local (Metycaine) anesthesia. Urine was collected through a multiholed, soft, rubber catheter, the bladder being washed out at the end of each clearance period by the injection of sterile, distilled water followed by air. Collection periods varied with urine flow, and usually were of ten to twenty minutes' duration.

The chemical analyses of the urine and serum or plasma were performed using the following methods: sodium, by the gravimetric method of Butler and Tuthill[9]; chloride, by Van Slyke's modification of Sendroy's iodometric technic[10]; uric acid, by the method of Kern and Stransky[11]; and mannitol and para-amino hippurate by the usual methods of Smith and co-workers,[12, 13] after appropriate dilution of urine to ensure a mannitol U/P ratio of approximately one in the samples analyzed.

The clearance tests were performed on all patients in bed in the morning at least fourteen hours after the previous meal. Following the completion of three or more control periods, a 2 cc. dose of Mercuzanthin intravenously, or Thiomerin, intravenously or subcutaneously, was administered; the urine was then collected during consecutive clearance periods for two hours or until maximal diuretic response had been achieved.

In 3 patients, the effects of Thiomerin administered subcutaneously and intravenously on separate occasions were compared. The two procedures were performed at about weekly intervals to enable each patient to recover fully from water and salt depletion.

RESULTS

Table 1 presents data on the twenty-four hour urinary volume and chloride output of representative patients in congestive failure during control periods and after the administration of Thiomerin subcutaneously and other mercurials intravenously or intramuscularly. In most patients, the twenty-four hour urinary volume after subcutaneous injection of Thiomerin increased 1,000 to 1,500 cc. above control levels. At the same time, there was an approximately tenfold increase in chloride excretion which, in these patients on low-salt intake, averaged 0.2 to 0.3 grams (5.6 to 8.5 meq.) per twenty-four hours, during control periods. However, the responses in individual patients varied. Thus, in Patient M. I., whose daily urine volume and chloride output rarely exceeded 1,000 cc. and 0.3 grams, respectively, urine volume increased to 4,000 cc. with an associated chloride excretion of 12 to 15 grams. On the other hand, in Patient I. K., whose response to mercurials was reduced, increased chloride excretion occurred despite little or no increase in urinary volume.

Of special significance is the comparison between the effects of Thiomerin and other mercurials in the same patient at approximately the same weight. The data indicate that the diuretic effect of Thiomerin is not significantly different from that of other mercurials, including failure of response in some patients (for example, Patient A. B., table 2).

The effects on water and chloride excretion following the intravenous administration of Thiomerin to several noncardiac subjects are represented graphically in figure 1. For purposes of comparison, the response of a noncardiac patient to Mercuzanthin under similar conditions is included. On intravenous injection of Mercuzanthin there is a transient rise in water and electrolyte excretion which is probably due to the effect of the theophylline in the Mercuzanthin on both cardiac output and, consequently, glomerular filtration rate and renal plasma flow. Following this brief period these renal functions return to control levels; the parallel course and close proximity of this line to the thickened line in figure 1, representing the mean of the responses to Thiomerin, is evident.

Figure 2 illustrates the typical effects of intravenous Thiomerin on renal hemodynamics, water, sodium and chloride excretion, and uric acid clearance in a noncardiac patient. The sequence of events is as follows: during the first thirty to forty minutes after injection, no diuretic response is evident. Then, urine output and sodium and chloride excretion increase rapidly, reach a maximum at sixty to seventy minutes, and gradually decrease thereafter. As

TABLE 1.—*Effect of Mercurial Diuretics on Urine Volume, Chloride Excretion and Weight*

Patient	Mercurial	Urine Volume	Chloride Excretion	Weight	Weight Loss
		cc./24 hrs.	*grams/24 hrs.*	*Kg.*	*Kg.*
J. S., M. AsHD; H HD; Renal Arteriosclerosis	Control	1000–1500	0.3–0.5		
	Th	1200	1.38	70.2	0.6
	MH	2010	1.98	70.2	0.0
	Th	2470	3.63	72.0	1.0
	Th*	2090	2.21	72.2	0.0
I.K., M. RHD; Ascites	Control	400–800	0.1–0.2		
	Th†	910	2.66	52.5	0.0
	Th†	640	1.72	56.5	0.0
	Th	890	2.10	57.5	0.0
	Th	1000	2.15	58.5	0.0
	Th*	840	1.97	59.1	0.0
	MZ	1010	1.95	59.2	0.2
	Th	870	1.16	53.8	0.0
	Th	1030	1.82	54.9	0.2
S.K., M. AsHD Anginal Syndrome	Control	500–800	0.3–0.4		
	Th†	1780	5.63	53.8	0.3
	Th†	960	2.88	53.6	0.8
	Th	1680	8.36	53.6	0.8
	Th*	1280	5.17	52.8	0.8
	Th	1850	6.61	52.2	1.4
	Th	1500	4.69	51.0	0.6
	Th	1770	6.56	51.5	1.0
	Th	1870	7.58	51.4	1.4
S.C., M. AsHD	Control	700–800	0.09–0.1		
	MH	1800	—	69.8	0.5
	MH	1300	0.98	67.0	0.0
	Th	1590	3.39	68.0	1.1
	MH	990	0.57	65.2	0.4
M.I., M. Cong. HD H HD	Control	600–1000	0.1–0.3		
	MH	4780	14.0	54.5	3.3
	Th	3900	12.2	53.2	2.2
	Th	4450	15.1	54.0	3.0
	Th	3870	11.5	52.4	2.4
	Th*	3750	13.8	52.8	2.8
	MH	3940	12.1	53.0	2.6
	Th	4390	14.0	52.9	2.1
J.K., M. RHD Ascites	Control	800–1200	0.2–0.4		
	Th	1350	3.26	69.0	0.1
	MZ	1280	2.76	69.1	0.1
H.D., F. RHD HHD?	Control (Rice diet)	600–900	0.05–0.07		
	Th	1380	1.39	48.2	0.0
	Th	1950	0.5	48.6	0.2
	Control	800–1100	0.1–0.2		
	Th	1710	8.02	50.2	1.8
	Th	1000	1.62	51.0	0.2
	Th	2100	1.99	50.7	0.9
H.R., M. AsHD Renal Arteriosclerosis	Control	3000–3500	0.3–0.4		
	Th	4810	3.33	67.8	1.6
	Th	4920	2.84	68.4	1.0
	Th	4340	2.22	68.3	0.3
	Th	3270	2.03	68.2	0.2
	Th	5060	3.15	70.0	1.0
	MH	4490	1.33	69.2	0.0
	Th	4250	2.48	70.4	1.2
	Control	1300–1700	0.2–0.4		
	Th	1780	1.73	68.2	1.7
	Th*	2615	1.93	67.3	0.0
	Th	1230	1.38	69.0	0.0
	Th	2750	4.54	69.8	2.0
	Th	1840	3.38	68.7	0.9
	MH	2740	2.45	69.0	0.0

Th, Thiomerin, subcutaneous.
MH, Mercuhydrin, intramuscular. Dosage 2 cc.
MZ, Mercuzanthin, intravenous.

*, indicates intravenous injection.
†, indicates 1 cc. dose

a rule the changes in water and electrolyte excretion occur simultaneously. When electrolyte output exceeds one-tenth of a milliequivalent per minute, the excretions of sodium and chloride tend to rise and fall to an equal degree so that the two curves of excretion virtually coincide. Generally, no significant change in glomerular filtration rate or renal plasma flow occurs during the two to three hour period of observation following Thiomerin administration.*

In table 2 are summarized the data on renal hemodynamics and water and electrolyte excretion before mercurial administration and during the period of maximal diuretic effect. Generally, maximal increase in electrolyte and water output occurred together, but in 3 cases, maximal water diuresis occurred earlier.

The close correspondence between sodium and chloride excretion in these experiments is striking. In the noncardiac patients the time of maximal response on intravenous injection was fairly constant and occurred earlier than in the patients with congestive failure.

In table 2 are included the data on the three subjects (L. V., T. S., D. S.) in whom the subcutaneous and intravenous effects of Thiomerin were compared. The responses of one of these patients are illustrated in greater detail in figure 3. The chief difference between the

TABLE 2.—*Effect of Mercurial Diuretics on Renal Hemodynamics and Water, Sodium, and Chloride Excretion*

Patient	Mercurial	Time	G. F. R.		R. P. F.		Urine Volume		UV_{Na}		UV_{Cl}	
			Control	Hg	Control	Hg	Control	Hg	Control	Hg	Control	Hg
Non-Cardiacs												
		minutes	*cc./min./1.73 M²*				*cc./min.*		*meq./min.*		*meq./min.*	
B.P., F. Age 39,	Th iv	67	97.7	99.0	390	397	5.13	13.7	0.290	1.540	0.287	1.652
Anorexia nervosa	Th iv	70	68.7	68.7	—	—	1.97	10.7	.231	1.690	.240	1.665
Y.R., F. Age 23, Coarctation Aorta	Th iv	63	124	91.0	735	663	2.50	11.1	.207	1.277	.241	1.423
L.V., F. Age 26	Th sq	122	111	115	688	643	3.70	10.1	.149	1.408	.173	1.473
Granuloma C.N.S.	Th iv	70	112	109	718	615	8.0	21.9	.214	2.560	.243	2.670
T.S., F. Age 52	Th sq	117	74.2	78.3	395	388	6.10	13.0	.226	1.726	.245	1.735
Herniated Disc.	Th iv	88	83.4	75.8	435	368	5.0	10.0	.271	1.322	.284	1.360
D.S., F. Age 56	Th iv	132	87.0	64.6	446	362	8.60	8.20	—	—	.333	1.208
Chorea deg.	Th sq	167	84.2	69.0	447	350	6.52	9.03	—	—	.203	.926
A.W., M. Age 45 Cerebellar Disease	MZ iv	67	97.0	73.0	468	628	4.46	10.3	—	—	.453	1.293
Cardiacs												
A.B., F. Age 24 Rheumatic H.D., C.H.F.	Th iv	161	53.5	56.3	94	107	0.80	2.70	.001	0.021	.003	.062
G.R., F. Age 48 R.H.D.	MZ iv	172	63.6	63.8	180	181	4.50	10.6	.002	.273	.008	.402

Th. Thiomerin. 2 cc.
MZ. Mercuzanthin.
G.F.R., Glomerular filtration rate, as determined by mannitol clearance.
R.P.F., Renal plasma flow, as determined by para-amino hippurate clearance.
$UV_{Na, Cl}$, Urinary excretion of sodium and chloride respectively.
Time, Interval between injection of mercurial and maximal effect.

* In some patients, toward the end of the procedures, there were small but significant falls in both mannitol and para-amino hippurate clearances possibly secondary to salt and water depletion due to the mercurial action. However, the decreased para-amino hippurate clearance observed may be due not to a real decrease in renal plasma flow, but to a decreased extraction of para-amino hippurate which we have found, by renal vein catheterization, to occur after the administration of Thiomerin.[11]

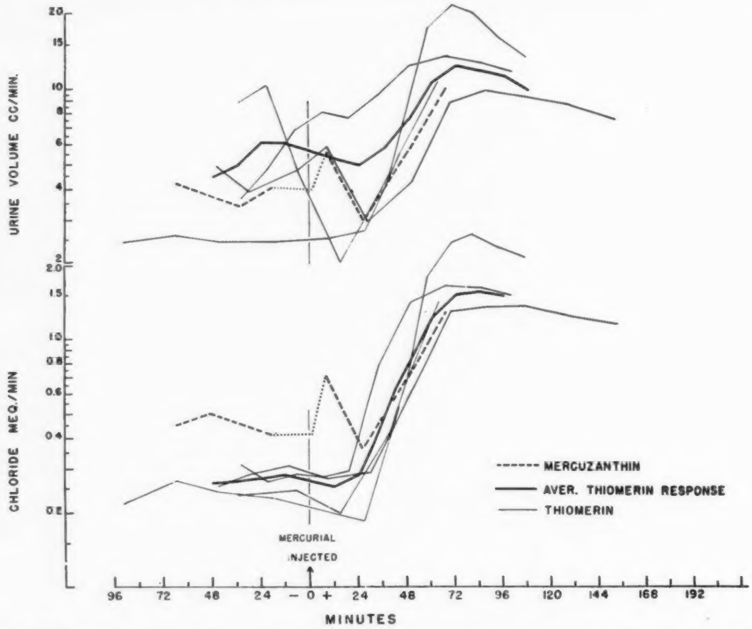

Fig. 1.—Effect of Thiomerin on water and chloride excretion in several noncardiac patients.

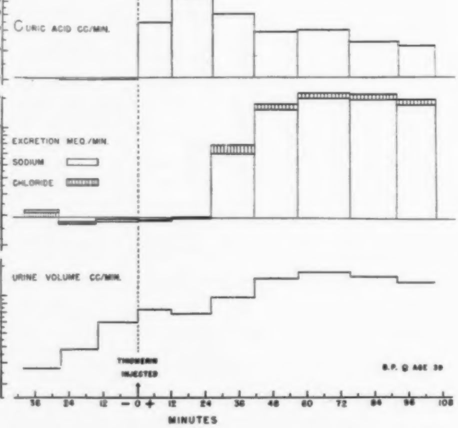

Fig. 2.—Effect of intravenous injection of Thiomerin on renal hemodynamics, water, sodium and chloride excretion, and uric acid clearance in a noncardiac subject.

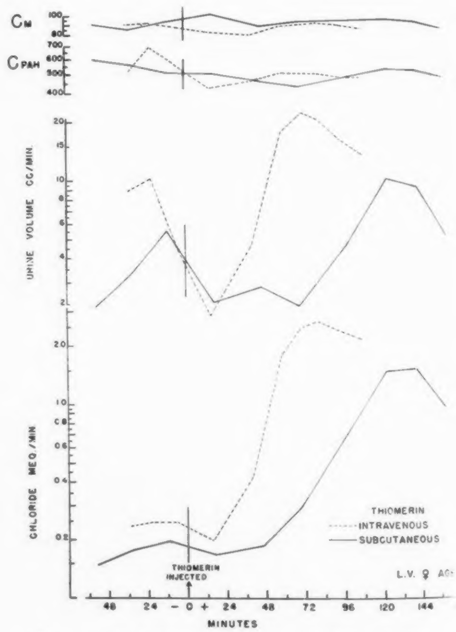

Fig. 3.—Relative effects of subcutaneous and intravenous injections of Thiomerin on water and chloride excretion in a noncardiac subject.

effects of the two routes of administration is the occurrence of diuresis thirty to fifty minutes earlier on intravenous administration. In this patient there also seems to be a more abrupt, somewhat greater, but less sustained rise of diuresis on intravenous administration than on subcutaneous injection. In the other 2 patients, however, there was little difference in the height of maximal response between the two routes of administration (table 2).

Uric acid excretion was measured in 8 patients prior to and following administration of Thiomerin and Mercuzanthin. The results are summarized in table 3. In figure 2, the changes in uric acid clearance in a noncardiac patient following intravenous Thiomerin are plotted with the other renal data. The data indicate a distinct rise and fall in uric acid excretion after both Thiomerin and Mercuzanthin administration. Since no rise in the glomerular filtration rate or plasma concentration of uric acid occurs, the increase in uric acid clearance probably is due to decreased tubular reabsorption. It is interesting that the maximal mercurial effect on uric acid excretion occurs long before that on water and electrolyte excretion. This difference may be due to greater sensitivity of the uric acid tubular transport mechanism to the action of mercurials.

In 4 patients, electrocardiograms recorded during the intravenous injection of Thiomerin revealed no changes attributable to the injection. Similarly, the examination of the urine of several patients who had had repeated injections of Thiomerin revealed no changes from the pretreatment findings, although certain thiols or their mercury complexes have been said to produce hematuria.[15] Apparently, a therapeutic dose, given twice weekly for four to six weeks, does not produce clinically demonstrable renal damage.

Subcutaneous injections of Thiomerin produce no more pain than does any subcutaneous aqueous injection. In more than 300 injections, no systemic reactions of any severity occurred. Two severe local reactions were encountered. The first followed the injection of 2 cc. of Thiomerin into a dependent, grossly edematous area of the thigh, and consisted of pain, redness, and ulceration. The effects were attributed to poor absorption of the injected material. The second occurred in a patient known to have a hemorrhagic diathesis, and consisted of a large area of ecchymosis which extended from the upper arm to the shoulder and elbow, with subsequent discoloration. It was accompanied by pain, induration and limitation of motion, but good diuresis. Both patients received Thiomerin subsequently without ill effect. The only other reactions observed were small subcutaneous nodules at the site of injection in some patients who had had repeated injections. In all but two instances, these were painless.

TABLE 3.—*Effect of Mercurial Diuretics on Uric Acid Clearance in Non-cardiac Subjects*

Patient	Mercurial	Time	G. F. R.		R. P. F.		Urine Volume		Uric Acid Clearance	
			Control	Hg	Control	Hg	Control	Hg	Control	Hg
		minutes	*cc./min./1.73 M²*				*cc./min.*		*cc./min.*	
L.V., F. Age 26, Granuloma,	Th sq	46	111	97.3	688	563	3.70	2.85	17.9	41.8
C.N.S.	Th iv	15	112	101	718	522	5.20	2.03	17.6	75.2
B.P., F. Age 39, Anorexia nervosa	Th iv	20	97.7	98.5	390	373	5.13	7.78	20.3	65.2
T.S., F. Age 52 Herniated Disc	Th iv	9	83.4	83.8	435	348	5.0	5.94	14.3	30.6
H.B., M. Age 57 Neoplasm	Th iv	8	98.3	99.3	—	—	15.0	12.8	37.9	63.0*
B.L., M. Age 26 Fracture	Th iv	15	63.2	62.4	—	—	18.3	19.5	15.2	44.7*
	MZ iv	60	57.2	67.7	283	—	5.23	13.7	8.7	19.3†
D.N., M. Age 26 Functional G.I. Disease	MZ iv	76	89.1	93.5	690	—	20.6	18.8	18.6	27.2*
E.K., F. Age 60 Bronchiectasis	MZ iv	32	103	127	370	—	11.0	24.8	20.7	35.6*
F.R., M. Age 64 Neoplasm	Th iv	20	55.5	61.1	295	—	7.77	9.84	23.8	57.0*

*, Performed during glucose T_M determination.
†, Performed during para-amino hippurate T_M determination.

Discussion

The marked qualitative and quantitative similarities between the changes in renal excretion of water, sodium, chloride, uric acid, mannitol, and para-amino hippurate after Thiomerin and Mercuzanthin injection suggest that the mechanism of action of the two mercurial diuretics is probably the same. Other studies,[16] indicating that the action of Thiomerin and Mercuzanthin on the renal tubular excretion of ammonia, titratable acidity, and para-amino hippurate, and glucose and phosphate reabsorption are similar, also support this conclusion.

Changes in urinary excretion without changes in plasma concentration of the excreted substances or in glomerular filtration rate must be secondary to altered tubular function. Thus, like other mercurials, Thiomerin is diuretic because of reversible toxicity to the renal tubules but, unlike other mercurials, exerts no manifest local toxic action on subcutaneous injection. Moreover, in a relatively small series of patients, none of the systemic reactions which are occasionally seen with other, usually intravenously administered, mercurials have been observed.

In the therapy of chronic congestive heart failure and other conditions in which there is gradual accumulation of fluid and salt, the advantages of a subcutaneously, and therefore, easily administered nontoxic mercurial diuretic are apparent. It is possible that repeated small doses of Thiomerin may produce a fairly continuous, sustained augmentation of sodium and chloride excretion and permit a more liberal sodium intake. For those patients who must continue activity, "eat out," or who must or desire to remain economically independent, such dietary freedom is of inestimable value to morale. Investigations are in progress to determine how effectively increased daily sodium and chloride excretion can be maintained by frequent injections of Thiomerin to cardiac patients on moderately restricted diets. Obviously, the lowest dosage required to avoid positive sodium and water balance should be administered. But the more general clinical application of such a regimen must await additional data on the excretion rates of Thiomerin to avoid the harmful effects of mercury accumulation, particularly in patients with reduced renal function. For example, Sollmann[17] mentions the potential danger inherent in mercury accumulation, wherein the sudden onset of bodily conditions favoring rapid reabsorption may give rise to mercury poisoning. However, there is evidence that the mercury of most organic mercurial diuretics is almost completely excreted in twenty-four hours. Studies on mercury excretion, following single and multiple injections of Thiomerin in man, are being conducted.

Because of the current emphasis on renal factors in congestive heart failure, it should be stressed that the sodium and water retention of cardiac patients is secondary to a more fundamental impairment in cardiac function. Therefore, therapy must be based on the accepted methods of improving myocardial function, such as digitalization and adjustment of activity to the physiologic capacity of the patient. At any stage of decompensation, mercurials are valuable for promoting loss of edema. However, as the patient's cardiac status deteriorates and chronic congestive failure develops, these diuretics and the low-salt diet become even more important.

Ultimately, the marked reduction in cardiac output may result in very severely reduced renal circulation. In this late stage of congestive failure, the very low glomerular filtration rate may be responsible, in part, for the lack of effect of mercurial diuretics. Thus, unless cardiac output, and therefore glomerular filtration, can be maintained, mercurials almost inevitably become ineffective, not because the patient develops any real "fastness" or acquired resistance to mercury, but because the tubular load of water and electrolyte is insufficient, after obligatory tubular reabsorption, to permit adequate excretion.[18] Until this stage is reached, mercurial therapy, like salt restriction, can help give the patient a longer period of relatively normal living and freedom from symptoms resulting from fluid retention. In short, although loss of edema and reduction of venous pressure, at times, may decrease the burden on the failing heart, the symptoms, not the disease itself, are treated. When an effective, more easily

administered and less toxic preparation such as Thiomerin becomes available, it should be added to the clinician's therapeutic armamentarium.

Conclusions

1. Thiomerin is a mercurial diuretic which can be safely administered subcutaneously.

2. The diuretic efficacy of subcutaneously injected Thiomerin is comparable to that of other mercurial diuretics administered intravenously or intramuscularly.

3. Studies on water, sodium, chloride, uric acid excretion, and glomerular filtration rate and renal plasma flow indicate that Thiomerin, like other mercurials, acts by decreasing tubular activity.

4. More extensive clinical study of the use of Thiomerin in relation to dietary salt intake in cardiac failure is indicated.

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The Prolonged Use of an Oral Mercurial Diuretic in Ambulatory Patients with Congestive Heart Failure

By Joseph B. Vander Veer, M.D., Thomas W. Clark, M.D. and David S. Marshall, II, M.D.

Tablets of an oral mercurial diuretic were utilized in the management of patients with severe congestive failure over a prolonged period of time. The need for parenteral mercurial diuretics was eliminated or greatly decreased by this therapy. The individual dosage was established by clinical trial. Minor toxic effects were encountered in several patients but in all instances it was possible to resume the therapy. Severe toxicity was not seen and there were no symptoms of salt depletion. Ease of administration, a more sustained diuresis, and good patient cooperation are advantages of this type of therapy.

THE MOST effective diuretic agents which we have today, organic mercurial compounds, were introduced by German investigators in the early 1920's. These compounds are effective in promoting diuresis in over 90 per cent of edematous patients when given intravenously or intramuscularly. In recent years they have been found to promote satisfactory diuresis when given orally.[2] The diuretic effect of mild mercurous chloride (calomel) has been recognized for many decades and used for this purpose in Addison's pill. Because its action was uncertain and because adequate dosage caused untoward effects such as diarrhea, stomatitis, albuminuria, and hematuria, the drug was not wholly satisfactory.

The first clinically valuable organic mercurial compound, Novasurol, was introduced by Zeiler[3] in 1917 for the treatment of syphilis. Linking mercury with an organic compound reduced the undesirable effects of mercury while preserving its antitreponemal action. In this form, it was found possible to give the drug parenterally. The strong diuretic action of the compound was soon observed,[4] but was unsuitable for general use because of its undesirable effect on the kidneys.[5] In 1924, Bernheim[6] introduced Salyrgan, a more powerful and less toxic diuretic than Novasurol. Further research resulted in the preparation of another mercurial compound, Novurit or Mercupurin. It was introduced in 1928 by von Issekutz and von Veghn,[7] who claimed the drug to be less toxic than Salyrgan. They found that by combining the xanthine, theophylline, with Salyrgan the diuretic effect of the mercurial was augmented and untoward reactions at the site of injection and in the kidneys were reduced. These benefits were amply substantiated in the observations of deGraff, Nadler, and Batterman.[1] Theophylline is combined with the three organic mercurial compounds (Mercuzanthin, Mercuhydrin, and Salyrgan-theophylline) which are in common use today as parenteral diuretics. Although each of these drugs has its enthusiasts, there is no evidence that one is preferable to another under all circumstances.

The mercurial-theophylline compounds are reliable, powerful, and safe diuretics when given parenterally in office, clinic, and hospital practice. There are many reports in the literature of their continued use for months or years; however, there are disadvantages and limitations to the parenteral administration of these preparations.[8] Administration usually requires the service of a physician. Pain at the site of injection is not uncommon, particularly when given intramuscularly. Reactions secondary to their potent and sudden diuretic effect are not unusual. These include muscle cramps, weakness, giddiness, and sometimes prostration. Digitalis toxicity may occur in digitalized patients following the prompt and copious diu-

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The oral mercurial diuretic, Mercuzanthin, used in these studies was supplied through the courtesy of Campbell Products, Inc., New York. Each tablet represents the concentrate of 0.74 cc. Mercuzanthin solution (brand of mercurophylline injection U. S. P.), equivalent to 0.030 Gm. mercury and 0.027 Gm. anhydrous theophylline.

resi- On rare occasions, sudden death has followed the intravenous administration of a mercurial diuretic. Administering the diuretic by rectal suppository has been attempted, but irritation of the rectal mucosa occurs frequently.[9]

In 1941 Batterman, deGraff and Rose[2] reported favorably on the diuretic effect of Salyrgan-Theophylline by oral administration. Previously there had been inconclusive reports from Germany on the similar use of Novasurol, Salyrgan, and Novurit (Mercupurin).[10] Since 1941 there have been other reports demonstrating that Salyrgan-theophylline and Mercuzanthin are effective diuretics when given orally.[11–14] In single doses they are not as potent as the usual intravenous or intramuscular dose; however, they are more powerful than the xanthines or the acid salts. The purpose of the present study has been to determine the usefulness of an orally administered mercurial diuretic in ambulatory patients with congestive heart failure when administered over a prolonged period of time. Particular attention was directed toward the value of this mode of administration in decreasing the need for parenteral mercurial therapy, in relieving patients of the signs and symptoms of congestive failure, in decreasing the need of hospitalization for heart failure, in observing patients for possible toxic effects coincident with the prolonged use of mercury, and in arriving at some idea as to the optimum daily dosage.

Material

A total of 34 patients was found suitable for final analysis. No patient was included in this study who had received the oral mercurial preparation for less than thirty days. Of the 34 patients, 27 had required parenteral mercurial therapy prior to using the oral drug. The remaining 7 had never received parenteral mercury. Thus, for the purpose of comparing the period on parenteral therapy with the period on oral therapy, the 34 patients were divided into two groups; those who had had a previous period of parenteral mercurial therapy and those who had not.

Five etiologic diagnoses were represented among the 34 patients and all patients had chronic congestive heart failure. Arteriosclerotic heart disease comprised the largest group and included 17 patients. There were 9 patients with rheumatic heart disease, 5 with syphilitic heart disease, 2 with hypertensive heart disease, and one patient with congenital heart disease (Lutembacher's syndrome). Hypertension was found in 16 patients. The average age was 58 years. The youngest patient was 19 years of age and the oldest 81 years. In the group studied, 23 were male patients and 11 were female.

Ambulatory patients, most of whom attended the Adult Heart Clinic of the Pennsylvania Hospital, were selected for study. The patients suffered from rapidly recurring edema due to chronic heart failure. Many had been followed for several years and had required parenteral mercurial therapy. With few exceptions, the patients had been digitalized and were instructed in a low sodium diet.

Method

All patients had complete blood counts, urinalyses, blood serology, and urea nitrogen determinations done at varying intervals while under observation. The urine and blood urea nitrogen were watched carefully for signs of renal damage which might be related to the mercurial therapy. An electrocardiogram and orthodiagram were done when the patient was admitted to the clinic and thereafter as indicated. Each patient was examined in the clinic at weekly or biweekly intervals. The physical examination, interval history, weight and vital capacity were recorded on each visit.

At the beginning of the study, patients were placed on a dosage schedule of 1 tablet of the mercurial diuretic daily. On this regimen, it was found that appreciable diuresis was not obtained for two or three weeks. For this reason and because the drug was well tolerated by the patients, the dose was subsequently increased to 3 and as high as 6 tablets daily. More rapid and pronounced diuretic effects were noted with the increased dosage. There was little tendency towards an increased intolerance to the drug.

If prompt diuresis was desired, the patient was started on 6 tablets daily (2 tablets three times daily). Satisfactory diuresis was usually evident in one to three days. This regimen was continued for three to six days and then reduced to a maintenance dose of two or three tablets daily. Occasionally patients were maintained on 6 tablets daily for as long as six weeks. Some patients, however, required no more than 1 tablet daily after the initial diuresis.

We found that the optimum daily maintenance dose had to be established individually for each patient by observing his clinical response. Seventeen patients required maintenance dosages of 1 to 3 tablets daily. Nine patients required doses varying between 3 and 4 tablets daily. The remaining 8 patients received dosages of 1 to 6 tablets daily, the optimum daily dosage varying considerably during the period of observation.

It is well known that ammonium chloride augments the diuretic effect of mercurial compounds. DeGraff and his co-workers employed this drug in most of their patients in conjunction with the mercurial therapy. As a rule, this drug was not given to our patients in order that the side effects of the drug might not be confused with toxic manifestations of the oral mercurial.

The average period of observation for 27 patients on parenteral mercurial therapy prior to using the oral mercurial was 290 days. The shortest observation period was fourteen days and the longest was 1092 days. Among the 34 patients who received the oral mercurial, the average period of observation was 284 days; the minimum was thirty-two days, and the maximum was 742 days. It was necessary to interrupt the oral therapy at one time or another in 10 of the 34 patients. These interruptions were for the following reasons: (1) possible drug toxicity; (2) failure of the patient to obtain the drug when clinic appointments were neglected; (3) the desire of the physician to determine the clinical progress of the patient following drug withdrawal; and (4) hospitalization of the patient. The 10 patients did not receive the drug for an average of eighty-three days in an average total observation period of 367 days. Medication given during hospital admissions were excluded in this study on ambulatory patients.

Results

The response of each patient receiving the oral mercurial diuretic was classified as good: fair, or poor. In evaluating the patient and placing him in the category deemed most applicable, the following questions were posed: (1) Were the clinical signs and symptoms of congestive failure improved, unchanged, or worse when the patient was receiving the oral mercurial as compared to the observation period when the patient received parenteral mercurial therapy? (2) Did the need for parenteral mercurial therapy decrease? (3) Did the need for hospitalization for cardiac reasons decrease when the patient received an oral mercurial diuretic? (4) Was the oral mercurial well tolerated by the patient and were there any manifestations of progressive renal impairment which might be attributed to mercury?

In the group of 27 patients who had previously been receiving parenteral mercurial therapy, 22 patients were classified as having good responses, 3 fair responses, and 2 patients were classified as responding poorly since they showed no improvement. Of 7 patients who had received no parenteral mercury prior to the oral preparation, 5 had good responses and 2 showed fair responses. None in this group did poorly. Thus, in the total group of 34 patients, 94.4 per cent were *benefited* while receiving the oral mercurial, and 79.4 per cent revealed responses which can be classified as clinically *good*. In addition to the beneficial results of the oral mercurial, the patients were more satisfied with this mode of administration. The weakness, muscular cramps, and prostration which occasionally follow parenteral mercurial therapy were not observed.

The following case report is cited as an example of the exceptional benefit derived from oral mercurial therapy.*

W. O., a 65 year old white woman, had arteriosclerotic heart disease, cardiac enlargement, mitral insufficiency, and auricular fibrillation. She was hospitalized with congestive heart failure for the first time in 1941. Despite digitalization at this time and maintenance digitalis therapy thereafter, further hospitalizations for heart failure was necessary in July, 1944, and November, 1945. Sodium restriction and the use of ammonium chloride were not sufficient to prevent edema and the patient received her first injection of intravenous mercury on December 15, 1945, with injections every two or three weeks thereafter. A gradual increase in the weight of the patient from 135 pounds in December, 1945 to a weight fluctuating between 150 and 156 pounds in May and June of 1947 occurred. The frequency of parenteral mercurial injections was increased in July, 1947 despite the marked weakness and muscular cramps which the patient usually experienced following the diuresis.

On November 3, 1947, the patient was started on an oral mercurial preparation, following which, she improved clinically and symptomatically. With the sustained diuresis, her weight decreased to a quite constant new low level (fig. 1). An initial daily dose of 3 tablets was given, and this was increased to 6 tablets daily after five days. A maintenance dose of 2 tablets daily was established as the patient improved. In December, 1947, following an unexplained weight increase, the daily dose was increased

* We are indebted to Dr. Arthur M. Rogers for permission to include the case report of this patient.

again to 6 tablets daily for four days. One parenteral injection of mercury was given, the first injection in six weeks, and the mercury tablets were reduced to 1 daily thereafter. The weight remained at the low level of 139 to 142 pounds without further parenteral therapy until the sudden death of the patient on January 20, 1948. A postmortem examination was not obtained and death was attributed to a cerebral embolus.

All 27 patients who had received parenteral mercurial therapy prior to the oral mercurial diuretic revealed a decreased need for parenteral therapy during the administration of the oral preparation. Previously, 12 of these patients required injections every five to thirteen days; 6 required injections every fifteen to twenty-three days; 4 received injections every thirty to forty-one days; and the remaining 5 received infrequent injections at intervals from forty-nine to eighty-four days. In determining the decreased need for parenteral injections in each patient, the first thirty days of oral mercurial therapy were

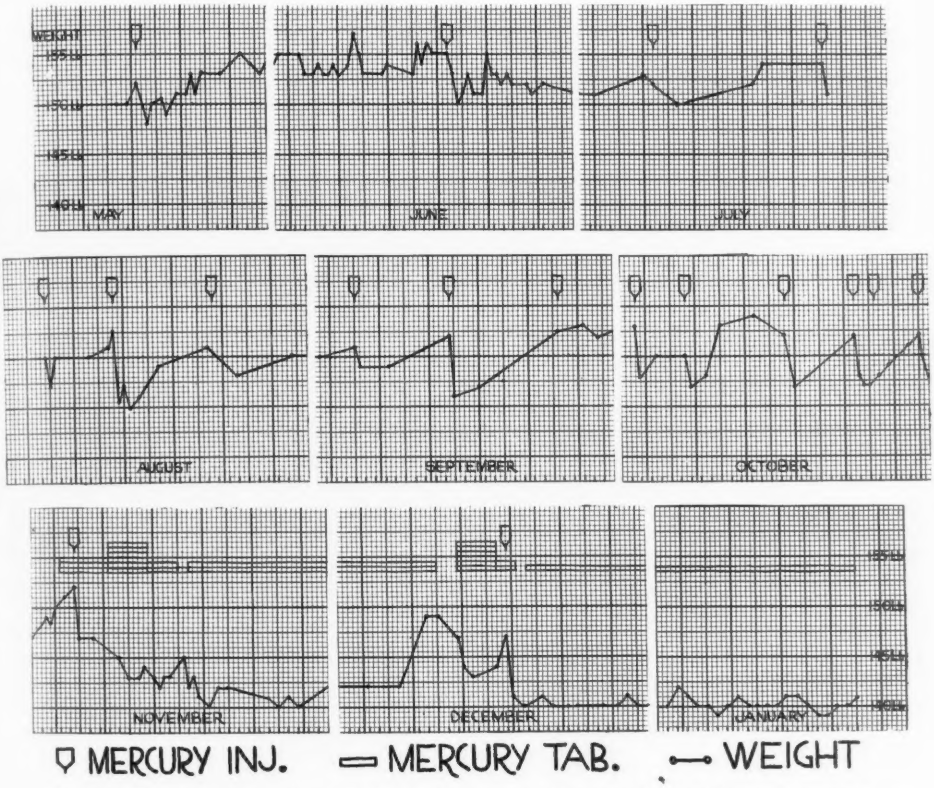

FIG. 1.—Weight chart on patient W. O., a white woman, 65 years of age, with severe anasarca secondary to arteriosclerotic heart disease and auricular fibrillation of several years' duration. Despite digitalis, ammonium chloride and limitation of sodium chloride her weight gradually increased as the result of edema formation. Some clinical improvement and reduction in weight followed an increase of the parenteral mercury injections which had been used occasionally for eighteen months prior to July 1947. Weakness and muscle cramps occurred after most of these injections. On November 3, 1947 oral mercurial therapy was started. This treatment caused a gradual drop in weight to approximately 10 pounds below the previous (average) level obtained by the parenteral therapy. The patient was greatly improved both subjectively and objectively during the subsequent period of nearly three months.

excluded to permit a reasonable lapse of time to achieve the fullest drug effect. Sixteen of the 27 patients required no parenteral therapy while receiving the oral preparation. Seven of these had previously required injections every five to eleven days. Seven other patients revealed a marked decrease in the need for parenteral mercury, and the 4 remaining patients showed only a slight decreased need. Thus, 85.1 per cent of patients previously requiring parenteral mercury showed a significant decrease in the need for this mode of therapy while receiving an oral mercurial preparation. Of the 7 patients who had no trial period on parenteral mercury, none required mercury injections while receiving the oral mercurial.

The comparative frequency of hospital days relative to the number of days that the patient was observed on parenteral mercurial and oral mercurial therapy was studied. Hospitalizations for cardiac reasons alone were considered. Twenty of the 34 patients were not hospitalized at any time. Nine patients requiring hospitalization while receiving parenteral mercury needed no hospitalization when receiving the oral preparation. Four patients showed a decreased percentage of time spent in hospital confinement while on oral therapy. Only one patient revealed an increased period of hospital days. Of the 7 patients who received no course of parenteral mercury, none required hospitalization during the period of study.

The patients were closely observed for signs and symptoms which might be attributed to toxic effects of the oral mercurial. For the purpose of the study, all such suggestive signs or symptoms were assumed to be related to mercury although it was recognized that similar manifestations might be due to other causes. Of the total group of 34 patients, 20 presented no suggestive signs or symptoms of drug toxicity. The remaining 14 patients presented signs and symptoms which might be attributed to drug toxicity. The most common manifestations were nausea, vomiting, and diarrhea, occurring singly or in combination. These occurred in 10 instances. Three patients developed stomatitis, and 2 others a Vincent's ulcer of the tonsil. Digitalis toxicity was observed in 2 patients. In 9 of the 14 patients, signs and symptoms suggestive of drug toxicity disappeared although the treatment was not interrupted. In none of the 14 patients did the reactions necessitate a permanent interruption of the oral mercurial therapy.

Serial blood urea nitrogen levels in 19 patients and urinalyses in 21 patients furnished no evidence to suggest progressive renal impairment. One patient who had been hospitalized for benign prostatic hypertrophy and uremia prior to the period of oral mercurial therapy was rehospitalized for uremia. This patient received 1 to 3 tablets of the oral mercurial daily for 105 days. Because of neglected clinic appointments, he received no oral mercurial therapy for three weeks prior to his hospitalization. The uremic state improved considerably but the patient died suddenly and unexpectedly in the fourth hospital week. His death was attributed to cardiac disease. Necropsy permit was not granted.

Five patients developed albuminuria while receiving the oral mercurial. Four of these 5 patients revealed only a faint trace to a trace of albumin. The uremic patient mentioned above progressed to a 3 plus albuminuria, which decreased to 1 plus as therapy was continued. Most patients revealed minor urine abnormalities at one time or another during the period of observation as might be anticipated in patients with advanced cardiac disease and congestive failure.

Ten of the 34 patients studied died. Six died during the course of oral mercurial therapy. Four died after periods of two to six months following discontinuation of the oral mercurial therapy.

Discussion

It was not the concern of this study to appraise the relative potency of oral and parenteral mercurial preparations. Undoubtedly mercurial diuretics are more rapidly effective when given by the parenteral rather than the oral route of administration. We have found, however, that the oral administration of an organic mercurial compound over prolonged periods of time is a useful, safe, and effective

method for promoting and maintaining diuresis in ambulatory patients with congestive heart failure. This was illustrated in the decreased need for parenteral mercury in all patients when receiving an oral mercurial preparation, and the absence of serious toxic manifestations.

Mild toxic reactions similar to those reported elsewhere were encountered in this study. Occasionally the drug was discontinued when such reactions occurred, but usually the therapy was continued. Nausea, vomiting, and diarrhea were always of transitory duration. It was difficult to be certain that mercury toxicity rather than transient gastroenteritis, digitalis toxicity, or disturbed physiology of the gastrointestinal tract secondary to congestive failure was the exact cause. In 3 patients who developed gingivitis, pre-existing pyorrhea had been observed. By periodic urinalyses and blood urea nitrogen determinations, the patients were observed for renal damage. Batterman, DeGraff, and Schorr reported 2 cases of uremia which were apparently related to an oral mercurial. We are not certain, in the single case of uremia which we encountered, that the oral mercurial was responsible, particularly in view of the previous uremic history of the patient. Minor evidences for renal damage were not considered to be of sufficient significance to warrant interruption of the therapy. In keeping with advanced cardiac disease, many patients in this study revealed impaired renal function as evidenced principally by albuminuria and urea nitrogen retention.

While receiving the oral mercurial preparation, the patients in this study impressed us as maintaining a more constant diuresis and more stable weight than when receiving parenteral mercurial therapy. Symptoms of hyponatremia, seen occasionally with parenteral mercurial therapy, were not present in patients receiving the oral mercurial drug. A more constant and sustained relief from the symptoms of congestive failure was noted by most patients, in contrast to the fluctuating states of relative comfort and discomfort experienced when receiving periodic injections of parenteral mercurial preparations alone. Thus, it is understandable that the majority of the patients in this study preferred the mercurial tablets rather than parenteral mercurial therapy.

Summary

1. Thirty-four selected patients with chronic congestive heart failure were given tablets of an organic mercurial preparation in addition to digitalis therapy and restriction of sodium chloride.
2. Twenty-seven of these patients had previously received parenteral mercurial therapy. In 25 of these patients the need for parenteral therapy was eliminated or greatly reduced.
3. A greatly decreased incidence of hospitalization for cardiac reasons was noted during the period of study.
4. No serious toxic manifestations were observed.
5. Oral mercurial tablets are a valuable adjunct to the therapy of chronic congestive heart failure.

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The Straining Procedure as an Aid in the Anatomic Localization of Cardiovascular Murmurs and Sounds

By Harry F. Zinsser, Jr., M.D., and Calvin F. Kay, M.D.

Most heart murmurs diminish in intensity during straining. Those derived from the right heart and pulmonary circulation regain intensity immediately after straining. Those from the left heart and systemic circulation recover only after an appreciable delay. The murmurs of patent ductus arteriosus and of mitral stenosis each showed a modified, but characteristic response. These murmur changes were correlated with recorded dynamic cardiovascular changes produced by straining.

Certain commonly used diagnostic technics are based on the relationship of murmur intensity to the rapidity and volume of blood flow. By exercise, amyl nitrite, and other means, the general circulatory velocity is increased to accentuate murmurs. If the blood flow in the right side of the heart and pulmonary artery could be altered *differentially* from that in the left side of the heart and aorta, then the time of murmur accentuation should provide a clue to its anatomic origin. Such a differential alteration in circulatory dynamics is provided in the relaxation period immediately following cessation of voluntary straining.

In a previous study[1] the electrokymograph was tested as an apparatus for recording the acute circulatory disturbances produced by straining. A marked difference was shown between the recovery pattern of the aorta and that of the pulmonary artery (figs. 1–4). During straining the increase of intrathoracic pressure causes an immediate reduction of venous return to the heart. The output of the right heart decreases, the pulmonary reservoir is depleted, and the output of the left heart falls. With relaxation, the intrapulmonic pressure returns to the atmospheric level. The venous blood which has been dammed back peripherally now rushes first into the right side of the heart. The previously reduced pulsations of the pulmonary artery become vigorous at once, and the lesser circulation is restored. The output of the left side of the heart and the aortic pulsations become maximal only after refilling of the pulmonary blood reservoir. Thus, in the period of relaxation, there is a difference in the time of maximal volume flow in the two sides of the heart.

Based on these changes the following predictions were made: (1) Murmurs should be altered, becoming faint during straining and gaining intensity after relaxation. (2) Murmurs originating from the right side of the heart or pulmonary artery should become intensified very early following relaxation. (3) The restoration of intensity of murmurs arising from the left side of the heart or aorta should be delayed. (4) The differences in time of return of the two types of murmurs should be as definite as the differences in the recovery patterns of aortic and pulmonary arterial pulsations which are demonstrated in figures 1–4.

This investigation was undertaken to test these predictions and to study the behavior of murmurs and other sounds of cardiovascular origin during the straining procedure.

Methods

Numerous patients with murmurs of various types were tested in the wards and clinics, and it was quickly found (1) that the murmurs could, in most instances, be reduced in intensity by the straining procedure and (2) that the time of return of murmur intensity varied. In order to demonstrate these changes graphically, recordings were made, in various combinations, of the heart sounds, electrokymogram, electrocardiogram, and intrapulmonic pressures. In each of the patients selected as a subject for these recordings, the anatomic location of the murmurs seemed unquestioned. Some patients had the characteristic findings of acquired valvular dis-

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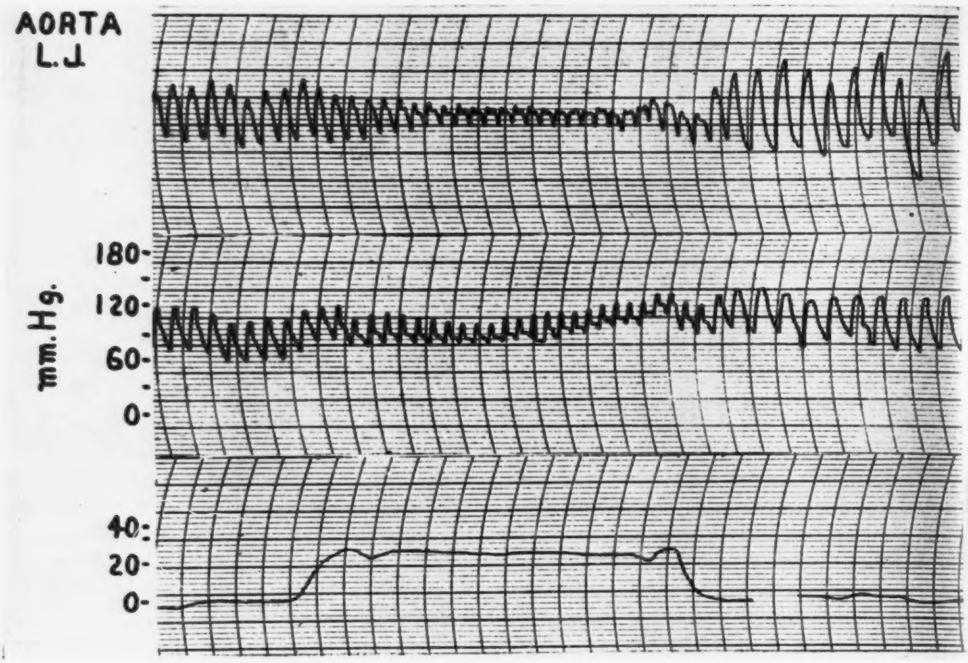

FIG. 1.—Normal subject L.J. Simultaneous recordings of aortic knob (upper), brachial arterial pressure (middle), and intrabronchial pressure (lower). During straining, aortic pulsations and pulse pressure are reduced, and pulse rate accelerates. After relaxation, return of amplitude of aortic pulsations and pulse pressure is gradual, and tachycardia changes to bradycardia after a few beats. (Figures 1–4 have appeared in a previous publication.[1])

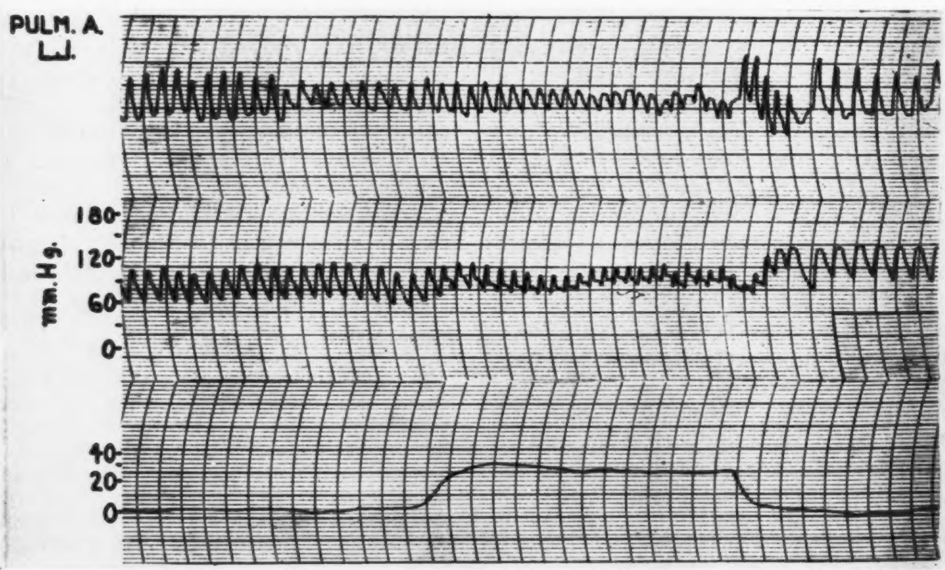

FIG. 2.—Normal subject L.J. Pulmonary artery pulsations (upper), brachial arterial pressure (middle), and intrabronchial pressure (lower). During straining, pulmonary arterial pulsations are reduced. After relaxation, maximal pulsations return immediately. Changes in pulse pressure and pulse rate as in figure 1.

ease. Others were proved to have pulmonary or peripheral arteriovenous aneurysms, or one or another of the various forms of congenital heart disease.

Recording Methods. The electrokymographic equipment used in this study was of the type described in detail elsewhere.[2, 3] Intrapulmonic pressure was recorded by a strain-gage manometer. The sound apparatus was of standard commercial type. All tracings were recorded on a Sanborn Tribeam instrument.

Investigative Procedure. When electrokymograms were feasible, the patient was seated before the fluoroscope and braces were applied to reduce extraneous movement. The microphone was strapped in position at the point of maximal murmur intensity. The straining procedure was a modification of the Valsalva maneuver, produced by blowing against a mercury manometer. On command, the breathing was arrested in a midrespiratory position and a short control period recorded. The subject then strained against the mercury column to a pressure of 20 or 30 mm. for a sufficient time to alter the murmur. He then relaxed but did not resume respirations until the poststraining recording was completed. Throughout this period the subject kept his glottis open. Employing this standard procedure, electrokymographic tracings of the pulmonary artery or aortic knob were recorded, along with the heart sounds, and intrapulmonic pressure or electrocardiogram. In certain instances the electrocardiogram was used as the timer instead of the electrokymogram.

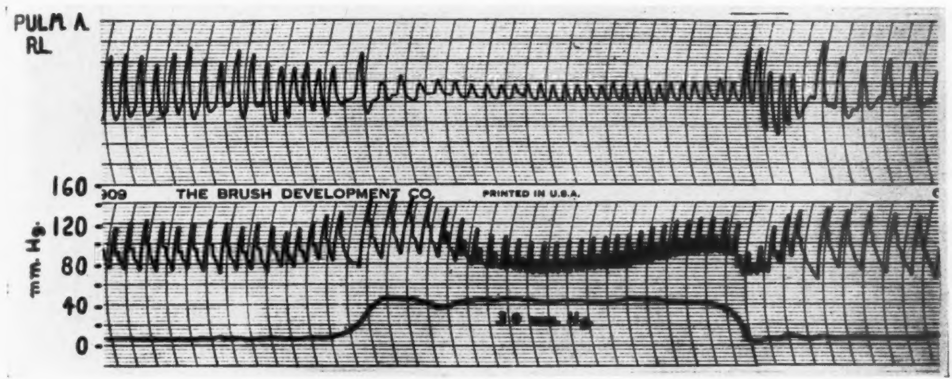

Fig. 3.—Normal subject R.L. Same as figure 1. Intrabronchial pressure illustrated is an overlay of actual recording.

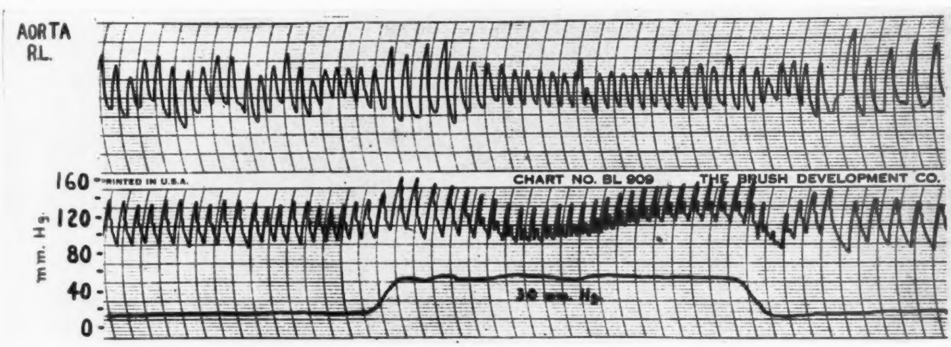

Fig. 4.—Normal subject R.L. Same as figure 2.

Such a procedure as that described above required a certain degree of patient cooperation. Some patients, especially infants and young children, could not be expected to follow the necessary instructions. Some were unable to do so because of dyspnea or weakness. Still others unknowingly supported the mercury column with oral compression, and ac-

tually raised their intrapulmonic pressure only momentarily, or not at all. This latter difficulty rarely caused serious trouble once we became aware of its existence. Finally, in about one individual of every 5 examined the murmur did not appreciably change in intensity despite evidently satisfactory cooperation.

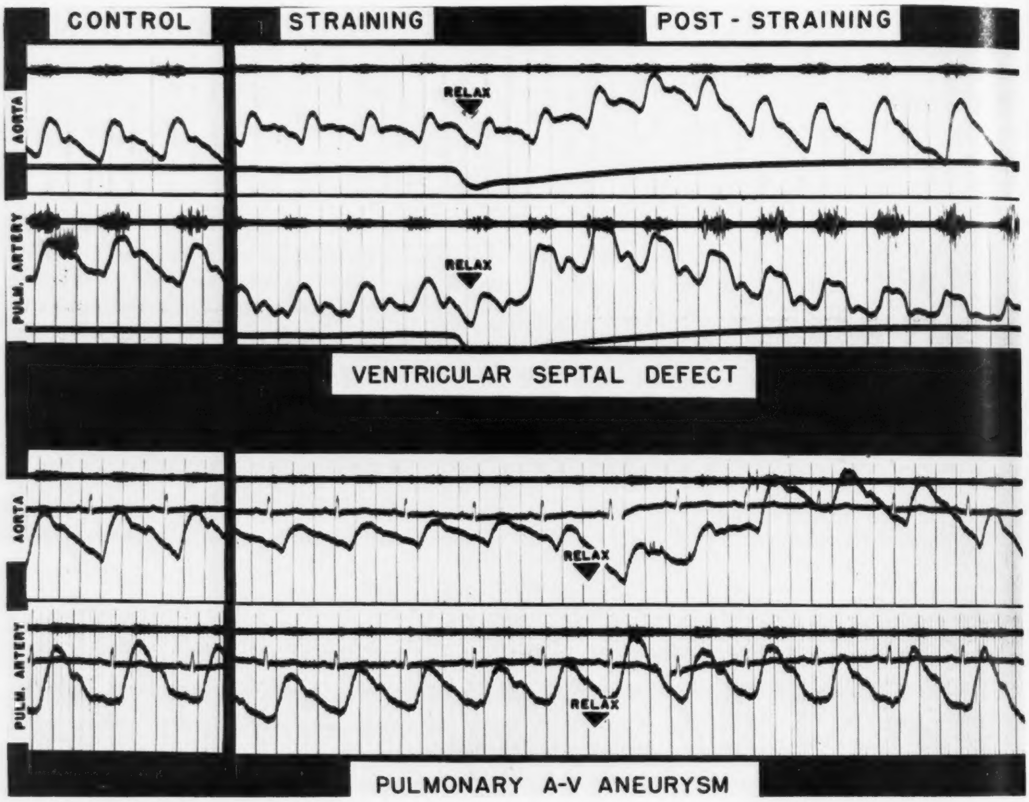

FIG. 5.—*A*, Ventricular septal defect. Sound recordings (upper), pulsations of aorta and of pulmonary artery (middle), and intrabronchial pressure (lower). The intensity of the systolic murmur is reduced during straining. After relaxation, the intensity returns progressively, in parallel with the recovery of amplitude of aortic pulsations. The return of maximal pulmonary arterial pulsation precedes the return of murmur intensity. Note also straining tachycardia and late poststraining bradycardia.

B, Pulmonary A-V aneurysm. Sound recordings (upper), electrocardiograms (middle), and pulsations of the aorta and of the pulmonary artery (lower). The intensity of the continuous murmur is reduced during straining. Murmur intensity recovers immediately upon relaxation, as does the pulmonary artery pulsation. Aortic pulsations show later return. (See also fig. 6.)

Thus, production of murmur changes was difficult or impossible in some individuals. Likewise, recording of audible changes was not always satisfactory. In this study we were constantly required to demonstrate objectively that which was often much more easily heard than recorded. For example, the fainter basal systolic murmurs and the higher-pitched aortic diastolic murmurs often gave characteristic responses to straining when heard with a stethoscope, but did not show very well on tracings. Under "Results," only those murmur changes which have been recorded objectively in patients with lesions of known anatomic origin are presented.

Results

Effect of Straining upon Murmurs

In general, the results bear out the predictions. When straining is effective, a definite

reduction in murmur intensity is the rule. In patients with uncomplicated right- or left-sided lesions the two types of poststraining response can be clearly differentiated. The murmurs of mitral stenosis and patent ductus arteriosus consistently show modifications of the typical pattern of left-sided response. Patients with advanced aortic insufficiency show the typical pattern of a left-sided murmur, but fail to show certain changes of pulse rate characteristic of straining. The murmurs of patients with complex congenital lesions show variable responses as would be expected.

Differentiation of Murmurs of Right and Left-Sided Origin. The ability of the straining procedure to aid in the anatomic localization of murmurs was tested in patients with murmurs of unquestionable right- or left-sided origin. Subjects with murmurs of *proved right-sided origin* were difficult to obtain due to the rarity of isolated tricuspid or pulmonary valve lesions. Thus, studies were confined to one patient with pulmonary arteriovenous aneurysm and one with a large mediastinal tumor compressing the pulmonary artery. The lower tracings of figure 5 show results in a patient with pulmonary arteriovenous aneurysm. The continuous murmur becomes less intense during straining and recovers immediately after relaxation. The electrokymograms confirm that this restoration of intensity coincides with the recovery of pulmonary arterial pulsations, and clearly precedes the return of aortic pulsations. These tracings exemplify the right-sided type of response expected for a murmur known to arise from a lesion of the pulmonary arterial tree. The right-sided murmur response is also shown in figure 6.

The control group of patients with *murmurs of proved left-sided* origin included subjects with the following conditions: aortic insufficiency, aortic stenosis, mitral insufficiency, mitral stenosis, uncomplicated ventricular septal defect, patent ductus arteriosus, peripheral arteriovenous shunts, and coarctation of the aorta (both for the precordial and collateral circulation bruits). When patients with these lesions were tested, records showed left-sided response patterns in which the murmur intensity was reduced during straining and recovered gradually after relaxation. (The murmurs of patent ductus arteriosus and mitral stenosis were subject to certain modifications which are discussed below.) This type of response is illustrated in the upper tracings of figure 5, which are taken from a patient with uncomplicated ventricular septal defect proved by cardiac catheterization. It is easily seen that this left-sided murmur recovers intensity in the late poststraining period, paralleling the increase in aortic pulsations recorded by the electrokymograph. The murmur changes are independent of the pulmonary artery pulsations which recover their maximal amplitude more rapidly after relaxation.

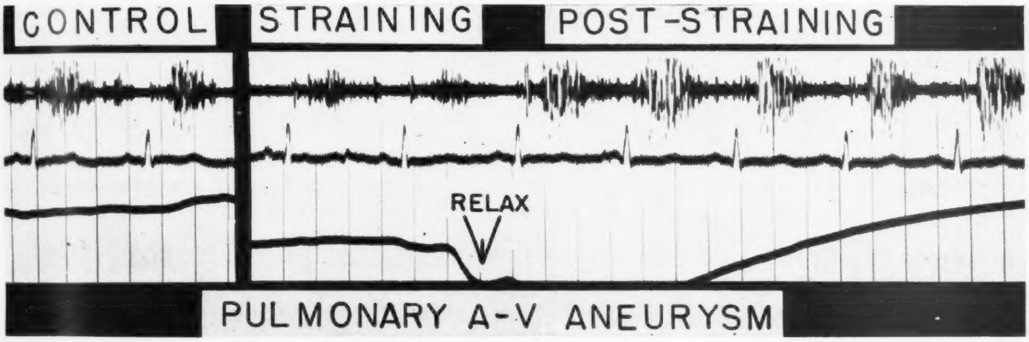

FIG. 6.—Same patient as in figure 5, *B*. Sound recordings (upper) with amplification increased in comparison with records of figure 5, *B*. Electrocardiogram (middle) and intrabronchial pressure (lower). Note recovery of murmur intensity immediately upon relaxation.

Modifications of the Standard Response. During the course of this study, certain conditions demonstrated variations from the usual re-

sponse to straining. In patients with advanced aortic insufficiency the expected changes in pulse rate were not seen. In other patients with mitral stenosis and patent ductus arteriosus, the typical pattern of left-sided response of the murmur was modified. These results deserve special mention and consideration.

ing were not found in these patients. Normally, the pulse rate increases steadily from the onset of straining. This tachycardia persists for several beats after relaxation, and is followed by a rather abrupt bradycardia. These rate changes are well demonstrated in figures 1, 2, 3, and 4, particularly in the latter two. They are not present in figure 7, and were not seen in six of seven other cases of aortic insufficiency. This absence of pulse change is presumably the result of an abnormality of the reflex mechanisms. We emphasize that the patients tested were considered to have advanced lesions, and had been chosen for their outstanding auscultatory and peripheral signs.

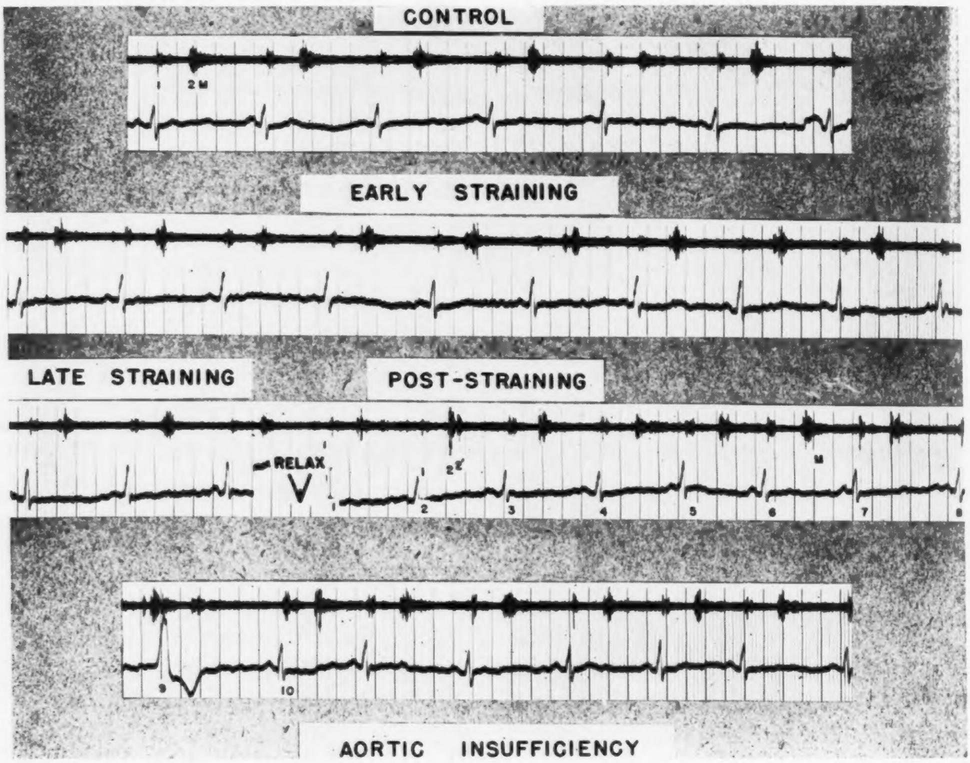

FIG. 7.—Aortic insufficiency. The diastolic murmur (M) diminishes in intensity during straining. It returns to maximal intensity on the sixth and seventh beats after relaxation. Neither straining tachycardia nor poststraining bradycardia is present. The second sound shows reduplication. The two components show independent recovery in the poststraining period. After relaxation, the first component is large in beat number 2; in beat 7 the components are equal; in beat 10 the second component is maximal (see text).

1. Aortic Insufficiency: The characteristic left-sided type of response was regularly observed in association with the murmur* of aortic insufficiency (fig. 7). While the murmur itself responded in a typical manner, the pulse rate changes characteristic of effective strain-

* In this murmur especially, changes easily heard with a stethoscope were often difficult to record.

2. Mitral Stenosis: This left-sided murmur tended to vary from the typical response pattern. In the early phases of the study when attention was directed particularly to the presystolic component of the murmur, most patients apparently failed to show a significant decrease of murmur intensity with straining. Successful production of rate changes during the procedure suggested that failure to strain could not account for the lack of murmur alteration. Indeed, these rate changes evidently explain the failure of the presystolic component of the murmur to show the usual strain pattern.

It is well known that an increase of rate accentuates a presystolic murmur. This accentuation is not primarily due to the general increase of blood flow, but is more closely related to the shortening of diastole that accompanies the increased rate. A presystolic murmur is louder with a short diastole, and softer or even absent with longer diastolic periods. This well-known phenomenon is demonstrated in the lower tracing of fig. 8, which shows the record of a patient with mitral stenosis and a loud presystolic murmur. During the recording, auricular premature beats oc-

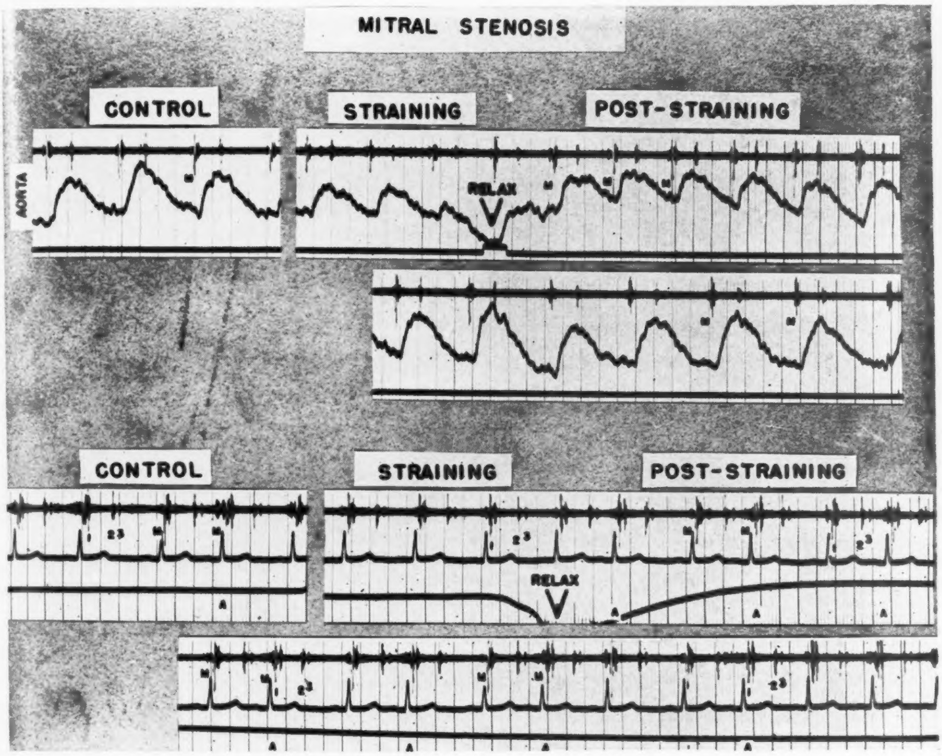

FIG. 8.—*A*, Mitral stenosis. The intensity of the presystolic murmur (M) is seen to correlate with changes is pulse rate. Contrary to the usual left-sided response, the intensity increases during the tachycardia of straining and decreases during the bradycardia of late poststraining (see text and fig. 9, *A*).

B, Mitral stenosis. The opening snap sound (3) remains unchanged throughout the procedure. The presystolic murmur (M) is consistently louder with the premature beats (A) than with the normal beats. Murmur intensity is reduced during straining. After relaxation, in the premature beats the murmur is easily seen, and its intensity is sequentially increased. Conversely, in the normal beats the murmur is barely detectable and does not appreciably increase in intensity (see text).

curred, and it is obvious that the presystolic murmur is much louder for the premature beats than for the beats following the longer pauses. Clearly, in producing a presystolic murmur, the effect of auricular systole is lessened after a long diastolic period. Such a period permits passive auricular emptying and ventricular filling to a point where auricular systole adds similar premature beats. However, the flow effect is minor, relative to the effect produced by the difference in duration of diastole.

Obviously, therefore, in the average patient with mitral stenosis, the rate changes produce effects opposing the blood flow changes. The tachycardia during straining and the bradycardia during relaxation will tend to neutralize,

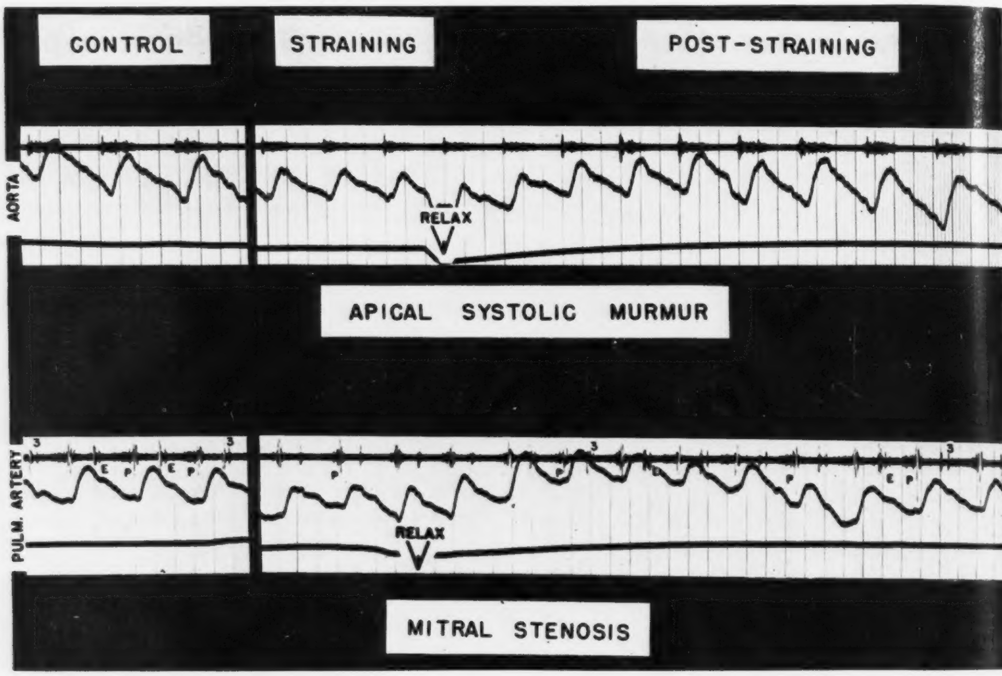

FIG. 9.—*A*, Mitral insufficiency. Typical left-sided response. The murmur intensity continues to increase during the bradycardia of the late poststraining period. (Contrast with Fig. 8, *A*.)

B, Mitral stenosis. The early diastolic component of the murmur (E) is reduced in intensity during straining and augmented in the late poststraining period in a typical left-sided response pattern. The changes in the presystolic component of the murmur (P) are also of the left-sided type, but are less conspicuous (see text). The opening snap sound (3) disappears during straining and returns on the third beat of the relaxation period.

relatively little impetus to blood movement. Thus, changes in rate, through their effect on the duration of diastole, appear to influence the intensity of presystolic murmurs to a greater degree than do changes in volume of blood flow during straining. That the increase of flow during the poststraining period has some effect can be seen by comparing the earliest premature beat of relaxation with sequential for the presystolic component of the murmur, the expected influences of altered blood flow. This is seen in the upper tracing of fig. 8 which shows the straining procedure in a patient with mitral stenosis. Straining has been effective, as evidenced by the development of characteristic rate changes and alteration of heart sounds. However, the presystolic murmur has not been decreased during straining, but is

somewhat decreased in the later relaxation period when bradycardia occurs. The upper tracing of figure 9 is included for comparison to demonstrate the typical left-sided response of a mitral systolic murmur. Note that this murmur continues to increase at the time of slowing in the poststraining period. The lower tracing of figure 9 shows the record of a patient with mitral stenosis in whom the intensity of the diastolic murmur decreases during straining and increases during later relaxation. Of the various portions of this diastolic murmur, the presystolic element shows less change than does the rest of the murmur. It is to be noted that the rate changes are less marked in this individual than in the others described above.

To recapitulate, in mitral stenosis, the behavior of the *presystolic component* of the murmur is variable. It may actually increase during straining and often does diminish in the poststraining period. This apparent paradox is a reversal of the effects expected to result from changes of blood flow on the left side of the heart. It is apparently a pulse rate phenomenon, contingent upon the fact that auricular systole is less effective in accelerating the flow of blood after a long diastole, when the ventricle has already been passively filled, than after a short diastole, when the ventricle is less well filled. The *early diastolic component* of the murmur of mitral stenosis responds in the characteristic left-sided manner.

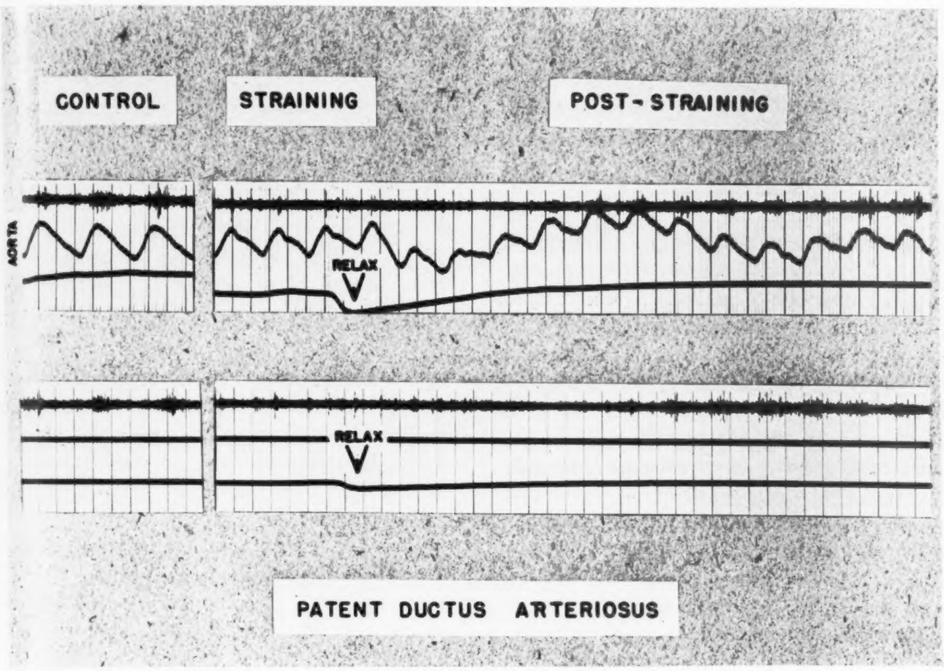

FIG. 10.—Patent ductus arteriosus. The continuous murmur is diminished in intensity during straining. It shows a still further reduction in amplitude in the immediate poststraining period, before regaining intensity in a typical left-sided manner.

3. Patent Ductus Arteriosus: In this condition the elevation of aortic pressure in the late poststraining period caused murmur accentuation in a characteristic left-sided manner. As an additional phenomenon, regularly observed in our three patients, the murmur became even fainter in the immediate poststraining period than it had been during late straining (fig. 10).

The sharp rise in pulmonary artery pressure immediately after relaxation had undoubtedly resisted the inflow of blood from the aorta. Theoretically, this pattern could occur in any patient with a murmur originating from a left to right shunt, but was definite only in the patients with patent ductus arteriosus. In patients with ventricular septal defect, a similar phenomenon was suggested in some records (uppermost tracing of fig. 5), but was not a consistent or clear-cut finding.

Effect of Straining Upon Murmurs in Congenital Heart Disease. In certain patients with congenital heart disease, a study of the murmurs by the straining procedure is unsatisfactory. This has been especially true of individuals with cyanotic malformations and atrial septal defects, since those old enough to cooperate are often unable to strain because of dyspnea or weakness. Hence, in these particular lesions, the number of patients available for a control group is inadequate. Despite this inadequacy, some preliminary observations should be reported, pending further study.

In the *cyanotic group*, certain complex lesions may produce murmurs which cannot be distinguished by the straining procedure as clearly left- or right-sided in origin. The systolic murmurs of the tetralogy of Fallot and the Eisenmenger complex may not permit differentiation between that sound component arising from the ventricular septal defect and that produced on the pulmonary side. Five such patients have been tested, and the results were variable, as would be expected. Where the murmur was affected by straining, the intensity recovered partly early and partly late in post-straining.

Two patients with the tetralogy of Fallot were studied postoperatively *after anastomoses of the Blalock type*. The continuous murmurs of the anastomoses were not decreased in intensity during straining, preventing any demonstration of a recovery pattern. While murmurs originating from a peripheral artery ordinarily give a left-sided pattern, in these patients the aorta itself receives considerable right-sided blood and the pattern should therefore be correspondingly altered. These two patients failed to cause murmur alteration despite apparently adequate efforts to strain. A patient with atrial septal defect similarly failed to produce murmur changes. These observations have led us to speculate upon possible mechanisms by which one could account for temporary maintenance of blood flow at the site of murmur origin despite a reduction in venous return of peripheral blood to the right atrium. The suggested explanations have had varying degrees of plausibility.*

In contrast to other types of congenital lesions, patients with patent ductus arteriosus, uncomplicated ventricular septal defect, and coarctation of the aorta have proved very satisfactory for study. These murmurs show a characteristic left-sided response pattern with the modification in patent ductus arteriosus as discussed above.

Effect of Straining upon Cardiovascular Sounds Other than Murmurs

Phonocardiograms made during the straining procedure show that heart sounds are also altered, becoming fainter during straining and regaining intensity following relaxation. This finding may prove of considerable practical value in the study of the various so-called "extra" heart sounds. While the present experiment was directed primarily toward the investigation of murmurs, certain observations were made regarding other sounds of cardiovascular origin. These results will be mentioned only briefly here, and will be subjected to further study.

1. *Split Heart Sounds.* If split second heart sounds arise from asynchronous closure of the left and right valves, then the pattern following straining will show differences in the recovery of the two components of the split sound.

* For example, in atrial septal defect, the volume of blood shunted from the left to the right atrium might increase during straining to compensate for diminished venous return from the periphery. As a result, blood flow through the right side of the heart and pulmonary artery would be sustained sufficiently to prevent a significant change in the murmur. The reservoir of the enlarged pulmonary vascular bed could constitute a source for such a flow. Obviously, this maintenance of flow could continue only briefly, but might delay the reduction of murmur intensity beyond the capacity of the subject to maintain effective straining.

This is seen in figure 7, where, following relaxation, there is an immediate increase of the initial component of a split second sound. Subsequently this first component subsides, and the second component increases in intensity. It is believed these changes indicate that the initial component of this split second sound was of pulmonary semilunar origin.

Certain studies by Wolferth and Margolies[4, 5] were concerned with the nature of splitting of the first heart sound. They concluded that "(1) the split first sound has a right ventricular and a left ventricular component, and that (2) separation of these components is due to asynchronism in certain early phases of cardiac contraction in the two ventricles." When tested by the straining procedure, split first sounds show a difference in recovery of the two components. This demonstrates that the components are of separate origin and confirms the earlier work.

2. *Opening Snap Sound.* The mechanism of the opening snap sound (claquement d'ouverture de la mitrale[6]) has been studied by Margolies and Wolferth.[7] (This sound is often referred to as the third heart sound of mitral stenosis.) Their evidence is in accord with the hypothesis that the sound is produced by the sudden limitation of the opening movement of a stenosed mitral valve. This movement occurs when auricular pressure exceeds ventricular pressure, but before blood of significant amount flows from auricle to ventricle. Thus, the snap is heard following the second sound, and precedes by a short interval the earliest part of the diastolic murmur. The behaviour of the sound with straining is compatible with this theory of its production. If the sound depends on the sudden checking of a movement of the valve en masse, then there should be some element of "all or none," i.e., a "threshhold" where the valve will move with enough suddenness and force to cause the sound, and below which it will fail to produce this effect. As seen on the lower tracing of figure 8, there is an opening snap sound which not only fails to disappear during straining, but shows no significant decrease or increase during the procedure. In the lower tracing of figure 9, the opening snap sound has disappeared during straining, and returned on the third poststraining beat with almost the same intensity as on any subsequent beats. In some instances this sound has shown a decrease in intensity during straining, with or without disappearance of the sound. However, when it disappears and reappears, there seems to be a threshold effect rather than a more gradual change.

3. *Other Miscellaneous Sounds.* We have some evidence that other sounds (gallop sounds, systolic clicks, semilunar opening clicks, and physiologic third heart sounds) might be altered by the straining procedure so as to differentiate right and left origin in a manner similar to that described above for murmurs. However, further study of these various sounds is necessary before their behaviour during straining can be considered established.

Discussion

The dynamic alterations of the circulation in response to increased intrathoracic pressure are reasonably uniform and predictable. During straining, cardiac filling is impaired and cardiac output is diminished. After straining, the right side of the heart fills first, and the blood flow in the lesser circulation is promptly accelerated. Filling of the left side of the heart and restoration of the flow in the systemic circulation occurs only after an appreciable interval required for the restoration of the pulmonary blood reservoir. In these studies it is shown that variations of the intensity of murmurs conform to the dynamic physiologic changes. A reduction in intensity of all types of murmurs is the rule during the period of effective straining. When a definite reduction occurs, it is rarely difficult to differentiate the prompt return of murmurs arising in the pulmonary circulation from the delayed return of murmurs arising in the left side of the heart or systemic circulation. As described in the results, modified responses were characteristic of the murmurs associated with certain lesions.

This material is not easily adapted to quantitative analysis. Complete records were made on 38 subjects with a wide variety of cardiovascular lesions of known anatomic location. These were selected from a much larger number of individuals in whom the effects of straining

were evaluated as a simple clinical procedure. Selection was based upon the opinion of the examiner that the murmur was of suitable pitch and intensity to show on the records, that the changes induced by straining were sufficient to be easily demonstrated objectively, and that the particular lesion had not already been demonstrated repeatedly in our records. Most of our subjects had lesions of the left side of the heart and systemic circulation. Numerically, murmurs produced by uncomplicated lesions of the right side of the heart and lesser circulation are relatively rare. In this study, only 2 such subjects were recorded, one with a pulmonary arteriovenous communication, and one with a lung tumor compressing the pulmonary artery at its bifurcation. In addition, the "physiologic pulmonic systolic" murmur of children and young adults was repeatedly found to respond according to the right-sided pattern as heard with a stethoscope. Since this study was directed toward lesions of known anatomic origin, we rarely attempted objective records in these subjects, and when attempts were made, we had little success in recording the murmur, even in the control period.

In almost every textbook of physical diagnosis or heart disease, references are made to the influence of respiration upon one or another type of murmur. In the main, these references apply to changes produced by variations of the *anatomic* relations of the chest wall to the vascular structures. The accentuation of the murmur of aortic insufficiency in full expiration, and the appearance of some cardiorespiratory murmurs only in certain respiratory positions of the chest wall may be cited as examples of this anatomic relationship. References to murmur changes resulting from alteration of circulatory *dynamics* incident to respiration are much less frequent. For example, Moyer and Ackerman[8] describe a murmur of pulmonary arteriovenous communication which was loud during inspiration and barely audible in expiration. The physiologic basis for this variation is not discussed. White[9] believes that the "physiologic pulmonic systolic" murmur is probably associated with a dilatation of the pulmonary artery under the increased pulmonary artery pressure during full expiration or during the Valsalva experiment. Levine and Harvey[10] likewise refer to increased pulmonary artery pressure during the Valsalva experiment as the possible causative factor in the production of a systolic murmur in a patient with an undiagnosed heart disorder. Actually, both the net pressure[11, 12] and the stroke change in diameter[1] of the pulmonary artery are regularly reduced during straining, hence a *dynamic* basis for the murmur accentuations described by White and by Levine and Harvey is not apparent.

To our knowledge this is the first controlled study of the effects of straining upon murmurs. This method should provide a teaching exercise useful in the application of a complex physiologic response to problems in clinical medicine. It should provide a foundation for research studies of the mechanism of certain heart sounds of obscure origin. Finally, it should be helpful clinically in the anatomic localization of murmurs of uncertain etiology.

Summary

1. Patients with heart murmurs associated with a wide variety of cardiovascular lesions were subjected to a standardized straining procedure Heart sounds, border movements of the great vessels, intrapulmonic pressures, and electrocardiograms were recorded.

2. Murmurs were reduced in intensity during straining. The response after relaxation depended upon the anatomic location of the lesion. (a) Murmurs derived from the pulmonic circulation returned immediately. (b) Murmurs derived from the left side of the heart and systemic circulation returned only after an appreciable delay. (c) The presystolic component of the murmur of mitral stenosis and the murmur of patent ductus arteriosus each showed a characteristic modification of the left-sided response. (d) Murmurs associated with complex intracardiac shunts responded variably.

3. These changes in murmur intensity were correlated with the sequence of dynamic events during and after an increase in intrathoracic pressure.

4. Sounds other than murmurs were also affected, and a brief discussion of these is included.

5. Observations of the effect of straining upon murmurs and sounds should be useful in teaching and in the investigation of the nature and origin of obscure heart sounds and murmurs.

ACKNOWLEDGMENT

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The Relation between Electrocardiographic Evidence of Right Ventricular Hypertrophy and Pulmonary Arterial Pressure in Patients with Chronic Pulmonary Disease

By John B. Johnson, M.D., M. Irené Ferrer, M.D., John R. West, M.D., and André Cournand, M.D.

Detection of right ventricular hypertrophy during life has often been exceedingly difficult. In a group of 40 patients with pulmonary artery hypertension either at rest or during exercise, in whom right ventricular hypertrophy of varying degree could therefore be anticipated, an attempt is made to correlate the pulmonary hypertension and the electrocardiographic evidence of right ventricular hypertrophy.

IN RECENT YEARS, the progressive developments made in electrocardiography have stemmed not only from the clearer definition of the basic principles involved in the electrical excitation process, but also from an attempt to correlate the electrocardiographic findings with the underlying structural abnormalities. The introduction of the unipolar precordial and limb leads in particular have prompted extensive investigation into the problem of ventricular hypertrophy.

Until recently, right ventricular hypertrophy, especially in the early stages, has defied clinical detection in a large percentage of cases. It is not surprising, then, that an attempt to define such hypertrophy by electrocardiographic means has been repeatedly made. Patterns held to be typical of right ventricular hypertrophy have been reported by several investigators.[1–4] Correlation of these patterns with autopsy findings has also been reported.[4, 5]

No satisfactory method has been devised so far to evaluate the degree of hypertrophy in the right ventricle in patients during life. With the advent of the catheterization technic,[6] however, it is now possible to detect even early pulmonary hypertension in man. Hypertrophy of the right ventricle may be anticipated as a consequence of sustained pulmonary arterial hypertension; the extent of this hypertrophy depends largely upon the duration and degree of the hypertension.

From the clinical and experimental points of view, therefore, it would be of interest to know whether any correlation exists between the pulmonary arterial pressure and electrocardiographic evidence of right ventricular hypertrophy. In this report such a study has been undertaken in a group of patients with chronic pulmonary disease.

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Material for Study

The diagnoses in the 40 patients on whom this study is based included silicosis, silicotuberculosis, diffuse pulmonary fibrosis, obstructive emphysema, bronchial asthma, pulmonary arteriolar sclerosis, and pneumonectomy for suppurative disease of the lung or bronchogenic carcinoma. Patients with obvious mitral stenosis or left ventricular failure were excluded.

Procedure

Electrocardiographic studies were made during the course of an investigation of patients with chronic pulmonary disease in whom cardiopulmonary function was studied. The pulmonary arterial pressure was recorded by means of a Hamilton manometer, using the right heart catheterization technic. Mean pressure was determined by planimetric integration of the area under the pressure curves. The reference point for right heart pressures was taken 5 cm. below the sternal angle (angle of Louis). In some of the patients in whom the resting pulmonary arterial pressures were normal or only slightly elevated, these pressures were again recorded at intervals during a ten-minute period of moderate leg exercise. The upper limits of the pulmonary arterial pressure found in this laboratory

TABLE 1.—*Clinical and Physiologic Findings in Nine Cases of Chronic Pulmonary Disease with Pulmonary Arterial Mean Pressure Less than 15 mm. Hg**

Case	Diagnosis	Duration of Symptoms	RA/TC × 100†	Art. Oxy. Hb. Sat.	Pulmonary Arterial Pressures (mm. Hg)			
					At Rest		After Exercise	
					S/D	Mean	S/D	Mean
				%				
426. Male 61 yrs.	Post-pneumonectomy 10 mos.: for suppurative pneumonitis.	No symptoms	33	91	17/5	10		
424. Male. 54 yrs.	Post-pneumonectomy 6 yrs.: for tuberculous bronchial stenosis.	No symptoms	34	97	28/10	15	55/17	28
435. Male. 39 yrs.	Post-pneumonectomy 7 yrs.: for bronchiectasis.	No symptoms	31	95	23/7	12	34/10	18
491. Male. 21 yrs.	Post-pneumonectomy 10 yrs.: for lung abscess.	No symptoms	26	100	23/7	12	35/19	24
499. Female 18 yrs.	Post-pneumonectomy 12 yrs.: for bronchiectasis.	No symptoms	18	96	18/9	12	23/14	17
428. Male. 43 yrs.	Healed hematogenous tuberculosis for 1 year.	2 mo. before therapy	14	94	15/5	10	20/5	12
485. Male. 27 yrs.	Diffuse pulmonary fibrosis.	9 mo.	24	95	18/7	11	30/11	23
483. Female. 43 yrs.	Diffuse pulmonary fibrosis; pulmonary emphysema.	14 mo.	49	96	19/10	13	43/23	33
501. Female. 32 yrs.	Pulmonary granuloma, beryllium exposure.	5 yr.	19	96	24/9	15	26/9	18

* None of these patients had ever developed right heart failure.

† The ratio of residual air to total capacity (RA/TC × 100) in the normal lung is less than 35 per cent. A ratio above 35 per cent indicates pulmonary emphysema.

TABLE 2.—*Electrocardiographic Findings in Nine Cases of Chronic Pulmonary Disease with Pulmonary Arterial Mean Pressure Less than 15 mm. Hg at Rest*

Case Number	Precordial Leads							Mean Electrical Axis
	R/S Ratio				Onset of Intrinsicoid Deflection (Seconds)			
	V_{3R}	V_1	V_5	V_6	V_{3R}	V_1	V_6	
								degrees
426		0.50	6.00	12.00		0.013	0.050	+65
424		0.24	3.20	3.30	0.010	0.018	0.028	+6
435	0.17	0.17	5.20	16.00		0.017	9.041	+86
491		0.20		(24.00)†		0.014	(0.040)†	+103
499*	1.70	1.30		1.70	0.040	0.052	0.046	+83
428	0.22	0.26	12.50			0.023	0.044	+13
485	0.31	0.29	4.30	6.50		0.018	0.024	+84
483	0.16	0.16	0.17	4.20	0.015	0.015	0.033	+10
501	0.22	0.25	27.00	12.00	0.018	0.018	0.057	+60

* Case 499 with an rsR′ complex in V_{3R} and V_1 shows the only anomalous electrocardiographic findings in this group.

† V..

in normal subjects is 30/10 mm. Hg with a mean pressure of 15 mm.

The electrocardiograms were recorded immediately before and after catheterization by means of a Cambridge string galvanometer. The leads taken included standard limb leads, augmented unipolar extremity leads, and precordial leads V_{4R}, V_{3R}, and V_1 through V_6 using the central terminal of Wilson. The analysis of the electrocardiograms included measurement of the R/S ratio and the onset of the

TABLE 3.—*Clinical and Physiologic Findings in Twenty Cases of Chronic Pulmonary Disease with Pulmonary Arterial Mean Pressure 15 to 30 mm. Hg*

Case	Diagnosis	Duration of Symptoms	$\frac{RA}{TC} \times 100$*	Art. Oxy. Hb. Sat.	Pulmonary Arterial Pressures (mm. Hg)			
					At Rest		After Exercise	
					S/D	Mean	S/D	Mean
				%				
471‡. Female. 55 yrs.	§ Cor pulmonale, Bronchial asthma, Chronic bronchitis, Pulmonary emphysema.	20 yr.	35	83	30/13	20		
474. Female. 23 yrs.	Bronchial asthma, Pulmonary emphysema.	15 yr.	73	82	38/15	26		
441. Male. 51 yrs.	§Cor pulmonale, Bronchial asthma, Chronic obstructive pulmonary emphysema.	20 yr.		88	37/4†			
528.‡ Male. 52 yrs.	§ Cor pulmonale, Bronchial asthma, Chronic pulmonary emphysema.	20 yr.	48	91	35/15	24		
489. Male. 72 yrs.	Chronic obstructive pulmonary emphysema.	18 yr.	56	94	42/12	26		
526. Male. 49 yrs.	Chronic obstructive pulmonary emphysema.	10 yr.	36	85		23		
468. Male. 47 yrs.	§ Cor pulmonale, Chronic obstructive pulmonary emphysema.	4 yr.	73	83	37/17	23		
458. Male. 66 yrs.	Silicosis.	10 yr.	22	93	30/13	19	52/19	33
465. Male. 65 yrs.	Silicosis, Chronic obstructive pulmonary emphysema.	15 yr.	56	87	51/12	24		
496.‡ Male. 55 yrs.	§ Cor pulmonale, Silicosis, Chronic obstructive pulmonary emphysema.	"Several years"	43	91	28/12	18		
467. Male. 65 yrs.	Silicosis, Pulmonary emphysema.	2 yr.	37	96	33/11	20	54/20	36
423. Male. 46 yrs.	Silicosis, Chronic pulmonary emphysema.	14 yr.	50	94	30/13	21		
430. Male. 59 yrs.	Silico-tuberculosis.	20 yr.	39	96	29/13	18	35/13	24
515. Female. 47 yrs.	Diffuse pulmonary fibrosis.	2 yr.	26	96	32/12	21		
464. Male. 43 yrs.	Diffuse pulmonary fibrosis.	18 mo.	27	91	29/8	16		
463. Male. 72 yrs.	Postpneumonectomy 10 yrs.: for carcinoma of bronchus, Pulmonary emphysema.	None	44	93	30/13	19	44/24	31
443. Male. 59 yrs.	Postpneumonectomy 1½ yrs.: for carcinoma of bronchus, Pulmonary emphysema.	None	50	97	36/8	19		
521. Female. 22 yrs.	Scleroderma with pulmonary involvement.	3 yr.		98	32/13	20		
436. Male. 53 yrs.	Bronchiectasis.	13 yr.	43	93	25/8	16	49/12	27
451. Male. 51 yrs.	Fibrothorax following hemothorax.	5 yr.	38	98	30/11	20	46/17	28

* $\frac{RA}{TC}$ = Ratio of residual air to total capacity. † Right ventricular pressure. ‡ These patients also appear in table 5 at the time of the original study when the pulmonary artery pressures were very high. § Recent recovery from right heart failure.

intrinsicoid deflections in the precordial leads, the electrocardiographic position of the heart, and the mean electrical axis. The latter was determined by the Einthoven triangle analysis using the algebraic sum of the R and S waves in Leads I and III.

Electrocardiographic Criteria

The electrocardiographic criteria for the diagnosis of right ventricular hypertrophy used in this study are based on the findings of Wilson and associates,[1, 2] which were confirmed and amplified by Goldberger[3] and by Myers and co-workers.[4] According to these findings three general patterns have been described:

1. In the first pattern, characteristic changes are seen in Leads V_{3R}, V_1, V_5, and V_6.

(a) The ratio of the amplitude of R to S is greater than one in leads from the right precordium (V_{3R}, V_1, or both), while the corresponding ratio in leads from the left precordium (V_5 and V_6) was less than that from V_{3R} and V_1 and frequently less than one, with prominent S wave in V_6.

(b) The onset of the intrinsicoid deflection in the right precordial leads was late in the QRS interval and usually later than the onset of those from the left precordial leads. The onset of the intrinsicoid deflection is the time interval from the beginning of the QRS complex to the peak of the R wave. It is said to represent the instant the excitatory process, traveling from the endocardial surface, reaches the epicardial surface of the myocardium underneath the exploring electrode. In this study it was measured by projecting the QRS complex along with the time lines on a screen and measuring the time interval.

The onset of the intrinsicoid deflection in Leads V_{3R} and V_1 used in this study were as follows: in normals 0.01 to 0.023 second; in right ventricular hypertrophy 0.03 to 0.05 second; in incomplete right bundle branch block 0.05 to 0.075 second, and in complete right bundle branch block 0.075 second and above.

(c) Notching or double peaking of the R wave in Lead V_1 is absent except when the R wave is preceded by a Q wave.

(d) The total QRS time is less than 0.12 second.

TABLE 4.—*Electrocardiographic Findings in Twenty Cases of Chronic Pulmonary Disease with Pulmonary Arterial Mean Pressure 15 to 30 mm. Hg at Rest*

Case Number	Precordial Leads							Mean Electrical Axis
	R/S Ratio				Onset of Intrinsicoid Deflection (Seconds)			
	V_{3R}	V_1	V_5	V_6	V_{3R}	V_1	V_6	*degrees*
471*	0.16	0.13	10.50	22.00	0.023	0.015	0.053	0
474	0.40	0.36	4.20	5.50		0.022	0.028	+71
441	0.06	0.03	0.47	1.40		0.016	0.035	+105
528*†	(2.00)§	0.00	0.29	0.44	(0.047)§		0.019	+163
489	0.27	0.28	2.28	3.00	0.024	0.026	0.046	+85
526		0.35		2.00		0.014	0.021	+78
468		0.13	0.83	3.00		0.021	0.034	+60
458		0.18	19.00	20.00		0.015	0.042	+22
465		0.08		1.75		0.026	0.029	+110
496‡		1.00	0.78	1.20	0.061		0.016	+100
467		0.24	1.25	1.61		0.018	0.032	+98
423‡	0.33	0.25	7.00	10.00	0.066	0.071	0.024	+100
430	1.00	0.75	4.00	2.50		0.014	0.028	+54
515	0.35	0.32		15.00		0.019	0.030	+40
464	0.83	0.50	6.00	10.00		0.017	0.042	−8
463		0.14	3.80	2.30		0.010	0.027	−18
443		0.25	2.50	4.00		0.025	0.036	+68
521	0.06			12.00		0.013	0.030	+52
451		0.11	20.00	10.00		0.028	0.028	+44
436		0.08	5.00	4.00		0.018	0.027	+72

* These patients appear in tables 5 and 6 at the time of the original study when the pulmonary artery pressures were very high.

† The only case in this group showing electrocardiographic patterns of right ventricular hypertrophy. (See tables 5 and 6.)

‡ rsR′ complex in Leads V_{3R} and V_1.

§ V_{6R}.

TABLE 5.—*Clinical and Physiologic Findings in Fourteen Cases of Chronic Pulmonary Disease with Pulmonary Arterial Mean Pressure above 30 mm. Hg at Rest*

Case	Diagnosis	Duration of Symptoms	$\frac{RA}{TC} \times 100$*	Art. Oxy. Hb. Sat.	Pulmonary Arterial Pressure (mm. Hg)	
					S/D	Mean
				%		
507. Male. 38 yrs.	‡ Cor pulmonale, bronchial asthma, pulmonary emphysema	25 yr.	42	53	68/37	47
471. Female. 55 yrs.	‡ Cor pulmonale, bronchial asthma, polycythemia	20 yr.	35	60	64/29	44
528. Male. 52 yrs.	‡ Cor pulmonale, bronchial asthma, polycythemia, chronic obstructive pulmonary emphysema	20 yr.	59	61	71/36	49
529. Male. 48 yrs.	‡ Cor pulmonale, bronchial asthma, pulmonary fibrosis	20 yr.	54	63	74/32	46
413. Female. 60 yrs.	§ Diffuse pulmonary fibrosis	1 yr.	46	88	54/20	34
478. Male. 36 yrs.	§ Diffuse pulmonary fibrosis	3 yr.	40	88	60/19	32
452. Male. 49 yrs.	† Cor pulmonale, chronic obstructive pulmonary emphysema	5 yr.		90	45/21	31
490. Male. 65 yrs.	‡ Cor pulmonale, chronic obstructive pulmonary emphysema, pulmonary fibrosis, polycythemia	2 yr.	54	70	61/23	36
334. Male. 49 yrs.	‡ Cor pulmonale, chronic obstructive pulmonary emphysema, pulmonary fibrosis	2 yr.	55	77	110/7**	
487. Male. 54 yrs.	† Cor pulmonale, silicosis	18 yr.	52	89	43/19	34
496. Male. 55 yrs.	‡ Cor pulmonale, silicosis, chronic obstructive pulmonary emphysema	"Several years"	46	76	61/30	41
415. Male. 60 yrs.	‡ Diffuse pulmonary fibrosis, arteriosclerotic heart disease	3 yr.	43	93	63/30	46
469. Female. 42 yrs.	† Patent ductus arteriosus, pulmonary arteriolar sclerosis***	11 yr.		94	133/51	83
472. Male. 6 yrs.	§ Primary pulmonary vascular disease	6 yr.		90	91/41	62

* $\frac{RA}{TC}$ = Ratio of residual air to total capacity.
** Right ventricular pressure.
*** Confirmed by autopsy.
† Recent recovery from right heart failure.
‡ In right-sided heart failure.
§ History negative for right heart failure.

A typical illustration of this pattern can be seen in figure 5.

2. In the second pattern the characteristic findings are present in V_{3R} while Leads V_1 through V_6 show no changes suggestive of right ventricular hypertrophy. In this pattern Lead V_{3R} shows the characteristic prominent R wave, with a delayed onset of the intrinsicoid deflection. The S wave in

TABLE 6.—*Electrocardiographic Findings in Fourteen Cases of Chronic Pulmonary Disease with Pulmonary Artery Mean Pressure above 30 mm. Hg at Rest*

Case Number	Precordial Leads							Mean Electrical Axis
	R/S Ratio				Onset of Intrinsicoid Deflection (Seconds)			
	V_{3R}	V_1	V_5	V_6	V_{3R}	V_1	V_6	
								degrees
507	4.70	5.00		0.55	0.047	0.056	0.034	+166
471		0.14	1.30	2.80		0.011	0.029	+74
528	2.50	2.00	0.06	0.18		0.042	0.019	+162
529*	1.50	1.80		1.67	0.055	0.051	0.026	+110
413		0.17	1.10	3.50		0.015	0.026	+78
478		2.90	1.50	1.50		0.052	0.037	+104
452	0.41	0.30	1.20	1.10		0.021	0.014	+99
490*	1.10	1.00		2.40	0.062	0.066	0.036	+50
334		0.00		0.18		0.000	0.020	+144
487*	0.85	0.93	1.10	3.00	0.066	0.069	0.036	+74
496*	2.60	2.75	0.69	1.00	0.057	0.058	0.012	+100
415	3.50	2.60	0.80	1.30		0.044	0.021	+120
469	11.00	1.20	0.60	0.55	0.023	0.049	0.037	+106
472	7.50	1.95	0.65	0.42	0.022	0.034	0.019	−7

* rsR′ complexes in right precordial leads.

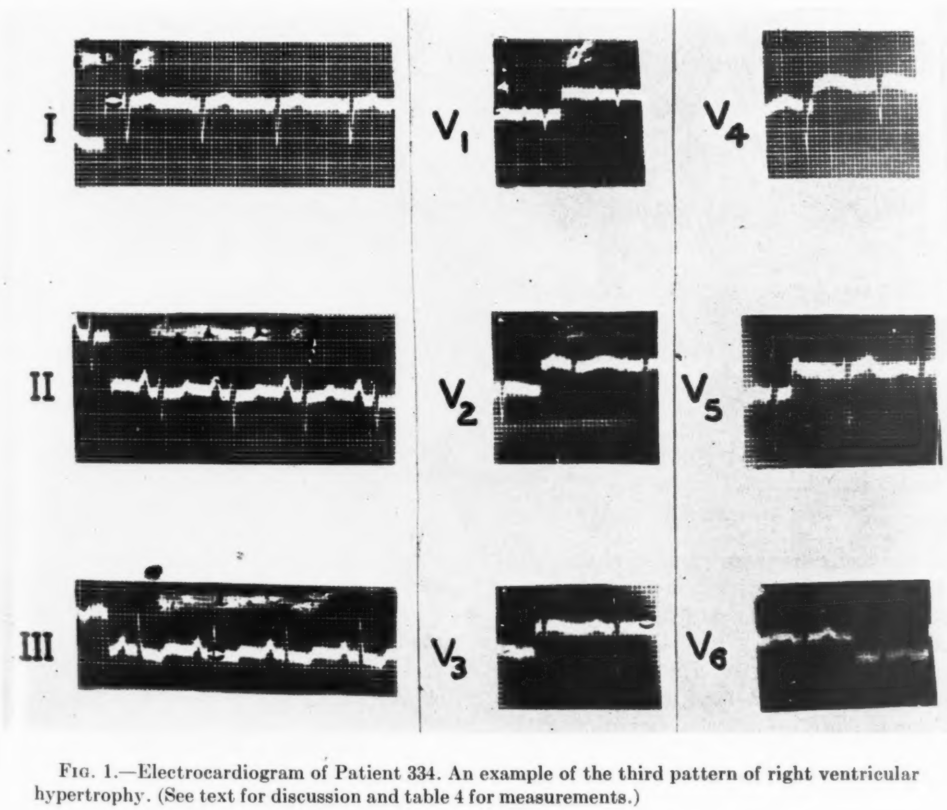

FIG. 1.—Electrocardiogram of Patient 334. An example of the third pattern of right ventricular hypertrophy. (See text for discussion and table 4 for measurements.)

Lead V_{3R} is absent and the QRS time is less than 0.12 second.

3. The third pattern, listed as presumptive evidence of right ventricular hypertrophy by Myers and associates,[4] is characterized by a prominent S wave persisting in leads over the left ventricle

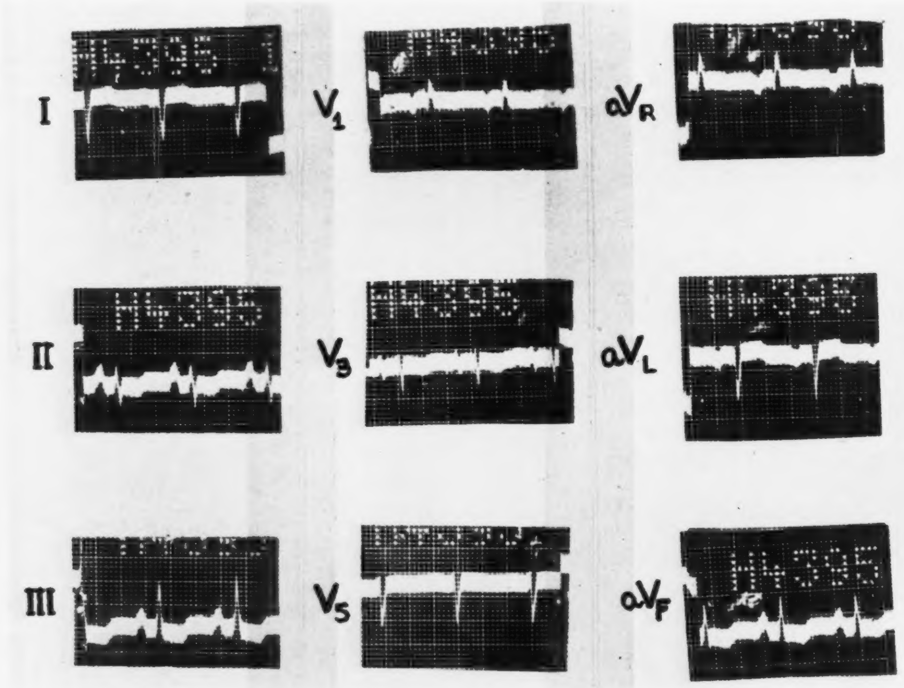

FIG. 2.—Electrocardiogram of Patient 334 made ten months following that of figure 1. Note the change from the third pattern (fig. 1) to the first pattern. In Lead V_1 the R/S ratio is 2.7 and the onset of the intrinsicoid deflection is 0.038 second.

(usually V_4 through V_6); a prominent R wave in Lead aV_R, whose amplitude was abnormally large in relation to that of the associated downward deflection, while leads from the right precordium are within normal limits.

of patients whose pulmonary artery mean pressure at rest was between 15 and 30 mm. Hg; and a group consisting of patients whose pulmonary artery mean pressure at rest exceeded 30 mm.

Results

In the preliminary examination of the material it was seen that, with a single exception, no right ventricular hypertrophy patterns occurred in patients whose pulmonary artery mean pressure at rest was less than 30 mm. mercury. This observation led to the arbitrary division of our cases into three groups: a group consisting of patients who had normal pulmonary arterial pressure at rest; a group consisting

Electrocardiographic Findings in Patients with Normal Pulmonary Arterial Pressures at Rest. The clinical diagnosis, pulmonary arterial pressures, electrocardiographic findings, and other significant data in this group of 9 patients are summarized in tables 1 and 2. Eight of these patients were studied both at rest and while doing moderate leg exercise. Six of the 8 had a distinct rise in the pulmonary arterial pressure above normal during the exercise period. The only significant anomaly in the electrocardiograms was found in Patient 499 and consisted of an rsR′ complex in Lead V_1 of the incomplete right bundle branch type. This patient had only a very small elevation of the

pulmonary artery mean pressure above normal with exercise. The other patients all showed normal electrocardiograms.

Electrocardiographic Findings in Patients with Pulmonary Artery Mean Pressure From 15 to 30 mm. Hg at Rest. This group consisted of 20 patients with various types of chronic pulmonary disease. The data on these patients are summarized in tables 3 and 4. It is to be noted from table 3 that several of the patients in this group had moderate to severe chronic pulmonary emphysema as indicated by an elevated ratio of the residual air volume to the total lung volume.[7] In 6 of these patients the pulmonary arterial pressure was also recorded during moderate leg exercise. During the exercise period the mean pressure rose from an average of 19 mm. Hg to an average of 30 mm. None of the three electrocardiographic patterns which have been used as criteria of right ventricular hypertrophy was found in 19 of the 20 cases in spite of the hypertensive state of the pulmonary circulation. Two of the 19 patients showed an rsR′ complex in Lead V_{3R} with a delayed

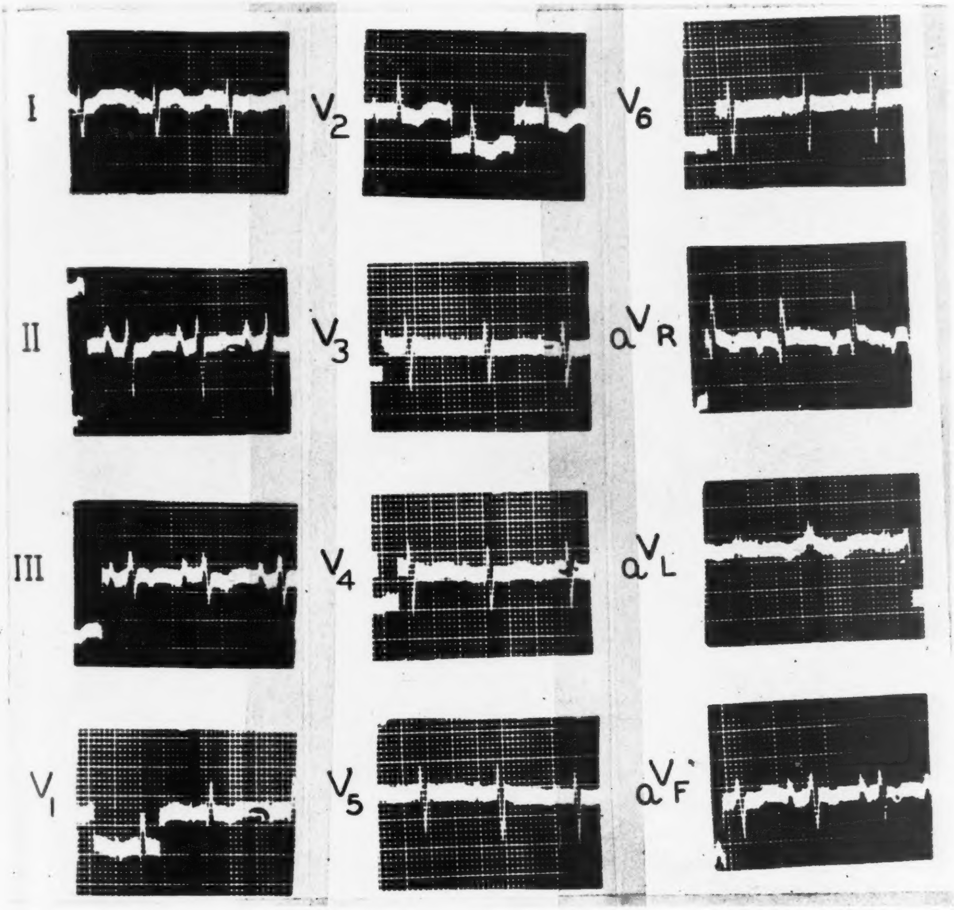

FIG. 3.—Electrocardiogram of Patient 490 shows the first pattern of right ventricular hypertrophy. R/S ratio of 4.0 and 0.6 in Leads V_1 and V_5 respectively, with corresponding onset of intrinsicoid deflections of 0.047 and 0.028 second.

onset of the intrinsicoid deflection (Patients 423 and 496). In the remaining patient (528), a pattern of right ventricular hypertrophy persisted after the pulmonary artery mean pressure had fallen from 49 to 24 mm. with treatment. This patient also appears in the final group of 9 patients with very high pulmonary arterial pressure and will be taken up later in the discussion.

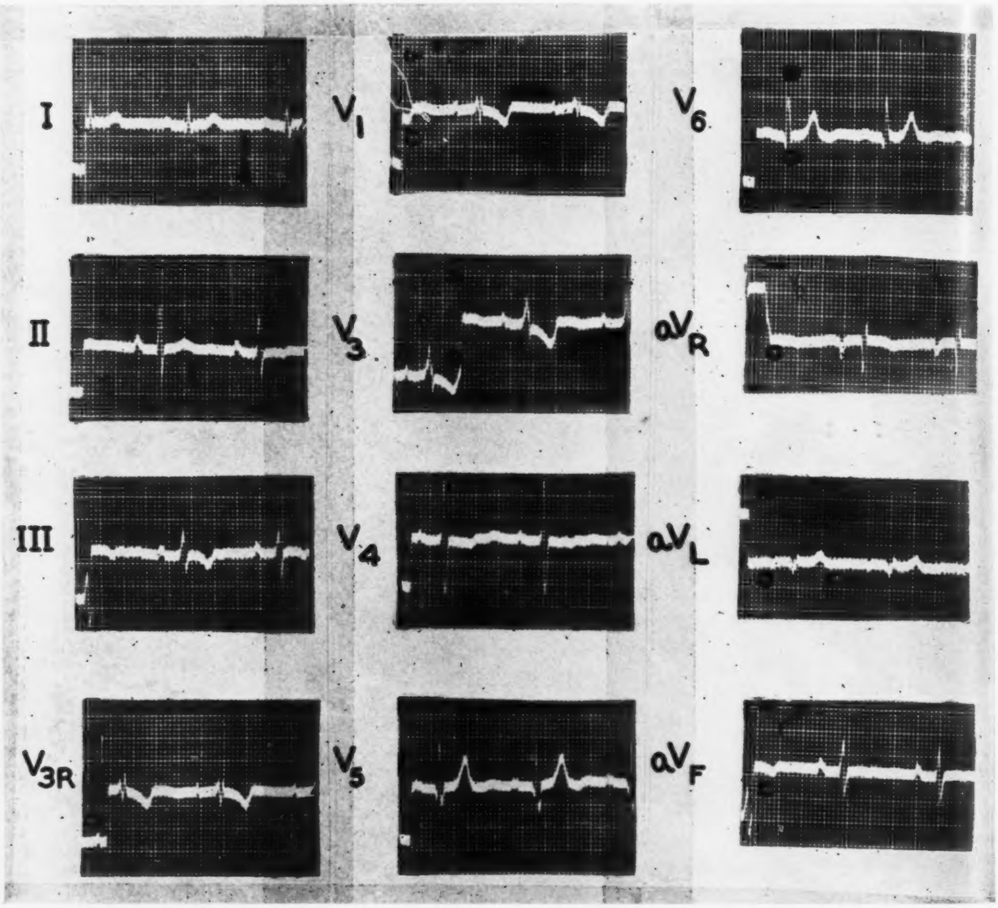

FIG. 4.—Electrocardiogram of Patient 490 made ten days following that of figure 3 at the time of cardiac catheterization. Note change from the first pattern (fig. 3) to the rsR′ pattern in the right precordial leads. (See table 6 for measurements.)

Electrocardiographic Findings in Patients with Pulmonary Artery Mean Pressure Exceeding 30 mm. Hg at Rest. The data on these fourteen patients are summarized in tables 5 and 6. None of these patients was exercised during the study. Eight of the 14 patients showed electrocardiographic patterns characteristic of right ventricular hypertrophy. Of these 8, 7 had electrocardiograms which were typical of the first pattern of the criteria. The other patient (334) showed the third pattern at the time of catheterization (fig. 1). An electrocardiogram of this patient made ten months later showed a change from the third pattern to that of the first pattern (fig. 2). None of the patients showed the electrocardiographic findings described in the second pattern. Of the remaining

6 patients, 4 showed electrocardiographic patterns with rsR′ complexes in the right-sided precordial leads. These findings were interpreted as indicating incomplete right bundle branch block. One of these 4 subjects (490), a patient with severe obstructive emphysema and pulmonary fibrosis, is of particular interest. On admission to the hospital he had severe arterial oxygen unsaturation, polycythemia, and right-sided heart failure. At that time the electrocardiogram (fig. 3) showed typical features of right ventricular hypertrophy (the first pattern of the criteria). About ten days later the electrocardiographic pattern (fig. 4) had changed to that of an incomplete right bundle branch block. The initial catheterization was performed after this change occurred and when the arterial oxygen unsaturation, polycythemia, and right heart failure were still severe. The pulmonary artery mean pressure at this time measured 36 mm. mercury. The incomplete right bundle branch block pattern has remained over a six months' period irrespective of whether the patient was in more or less severe right heart failure. The electrocardiograms of the remaining two patients of the group failed to show patterns either of right ventricular hypertrophy or of incomplete right bundle branch block (Patients 413 and 471).

Discussion

The data presented are of particular interest with regard to: (1) the degree of pulmonary arterial pressure elevation in relation to the electrocardiographic findings; and (2) the significance of the high incidence of the rsR′ complexes in the right-sided precordial leads in this group of patients with chronic pulmonary disease.

Eight of 9 patients with normal pulmonary arterial pressure at rest were exercised during the study. Six of the 8 developed an elevation of the pulmonary arterial pressure during the exercise period. This response probably indicates a restriction in the pulmonary vascular bed of these patients, since it has been demonstrated that the pulmonary arterial pressure does not rise significantly during severe leg exercise in the normal subject.[8] The electrocardiograms in this group of patients showed none of the three patterns which have been identified with right ventricular hypertrophy. Whether one would anticipate the development of right ventricular hypertrophy with the intermittent type of pulmonary hypertension seen in this group is open to question. In the second group, however, the pulmonary disease was more severe, as indicated by a significant pulmonary arterial hypertension present even at rest, and by the moderate to severe degree of arterial oxygen unsaturation in a large proportion of the cases. It appears probable that some patients in this group had hypertrophy of the right ventricle. The fact that the electrocardiograms showed none of the accepted patterns identified with right ventricular hypertrophy and the fact that no single additional electrocardiographic abnormality common to a majority of these patients was found, may substantiate the point of view expressed originally by Wilson and associates[2] that the electrocardiogram probably does not reflect moderate degrees of right ventricular hypertrophy.

It is clear from the data on the patients in the first and second groups that the absence of electrocardiographic patterns identified with right ventricular hypertrophy cannot be used to rule out the possibility of significant hypertension in the lesser circulation in patients with chronic pulmonary disease. However, in each of the eight patients who demonstrated electrocardiographic patterns of right ventricular hypertrophy the pulmonary artery mean pressures at rest exceeded 30 mm. mercury. Although the series is small, these data suggest that in patients with chronic pulmonary disease, the presence of an electrocardiographic pattern of the right ventricular hypertrophy type will be associated with a marked degree of pulmonary arterial hypertension. The data in this last group also indicate that in some cases pulmonary arterial hypertension of marked degree may not be associated with electrocardiographic patterns of the right ventricular hypertrophy type (Cases 413 and 471). In this connection it should be pointed out that in occasional patients with significant right ventricular hypertrophy as demonstrated at autopsy, recent electrocardiograms failed to

show patterns identified with right ventricular hypertrophy.[4]

In correlating pulmonary arterial hypertension and electrocardiographic findings, adequate consideration must be given to the anatomical position of the heart as it may be altered by surrounding pathological processes and by the presence of severe heart failure. Erroneous conclusions may be reached regarding the presence or absence of a right ventricular hypertrophy pattern in a given patient if the anatomic position of the heart is not properly evaluated. The complexity of this problem is well illustrated in Cases 471 and 528. Patient 471, a 55 year old woman, appeared to have a typical case of cor pulmonale with signs of right heart failure, marked degree of arterial oxygen unsaturation, severe polycythemia, and high cardiac output. Following repeated phlebotomy, digitalis therapy, use of bronchodilators and diuretics, the clinical state of the patient was improved and she became ambulatory. Pulmonary arterial pressure recording and electrocardiographic studies were made when the patient was in failure and after recovery. During this eight-week period the pulmonary artery mean pressure fell from 44 to 20 mm. mercury. At no time did the patient show characteristic electrocardiographic findings of right ventricular hypertrophy, but she did show significant changes in the electrical axis, the R/S ratio, and in the onset of the intrinsicoid deflections. The angle alpha changed from plus 74 to zero degrees; the R/S ratio in Lead V_6 increased from 2.8 to 22.0; and the onset of the intrinsicoid deflection in Lead V_6 increased from 0.026 to 0.053 second. In order to explain these changes it should be noted that during the first study when severe right heart failure was present, the heart was vertical with marked clockwise rotation about the longitudinal axis, and the transitional zone between the two ventricles was shifted far to the left (V_5). Presumably Lead V_6 of the first series of tracings was dominated by the potential variations of the right ventricle rather than the left, and thus accounted for the short onset of the intrinsicoid deflection in this lead. After full compensation the heart resumed a horizontal position with counterclockwise rotation. In the electrocardiogram of the second study the dominant influence in Lead V_6 probably is the left ventricle, which is responsible for the increased voltage of the R wave and the later onset of the intrinsicoid deflection.

The other case which illustrates the importance of the position of the heart on the electrocardiogram is Case 528. The patient, a 52 year old man with a history of persistent bronchial asthma of twenty years' duration, entered the hospital with severe right heart failure. Catheterization studies at that time showed a pulmonary artery mean pressure of 49 mm. mercury. The arterial oxygen saturation was 61 per cent and the patient had polycythemia. The electrocardiogram at this time revealed a typical pattern identified with right ventricular hypertrophy, a semivertical electrocardiographic position of the heart, and a mean electrical axis of plus 162 degrees (fig. 5). After two weeks of therapy, when the patient was greatly improved clinically, the second study showed a fall in the pulmonary arterial pressure from 49 mm. to 24 mm. and an increase in arterial oxygen saturation to 91 per cent. The electrocardiogram (fig. 6) showed no significant change in the electrocardiographic position or in the mean electrical axis, but the tall R wave and the large R/S ratio had disappeared from Leads V_1 and V_{3R}. In an attempt to explore the entire precordium over the right ventricle, additional precordial leads were taken from the third through the fifth intercostal spaces, medial to position V_{4R}. These still failed to show the previously demonstrated R wave and large R/S ratio. However, when precordial leads were taken lateral to position V_{4R} (V_{5R}, V_{6R}, V_{7R}) they revealed the characteristic large R/S ratio and the tall R wave with a delayed onset of the intrinsicoid deflection. These observations suggest that some mechanism other than hypertrophy of the free wall of the right ventricle is responsible for this pattern identified with right ventricular hypertrophy, as has been suggested by Kossman.[9] Although these changes occurred in the precordial leads the prominent S wave in Lead V_6 and the dominant R wave in Lead aV_R, usually found in electrocardiographic patterns of right ventricular

hypertrophy, remained characteristic in this patient during the entire period of study. As a result of this experience, it is proposed that at least one precordial lead should be taken at or to the right of V_{5R} in studying patients for patterns of right ventricular hypertrophy. Had no leads to the right of V_{3R} been taken, this tracing probably would have been classified as dence of right ventricular hypertrophy if leads to the right of V_{4R} are recorded.

The second point of discussion deals with the significance of the high incidence of the rsR′ complex in the right precordial leads in this group of patients with chronic pulmonary disease. In 6 of the 39 patients, rsR′ complexes in Leads V_{3R}, V_1, or both, with a total QRS time

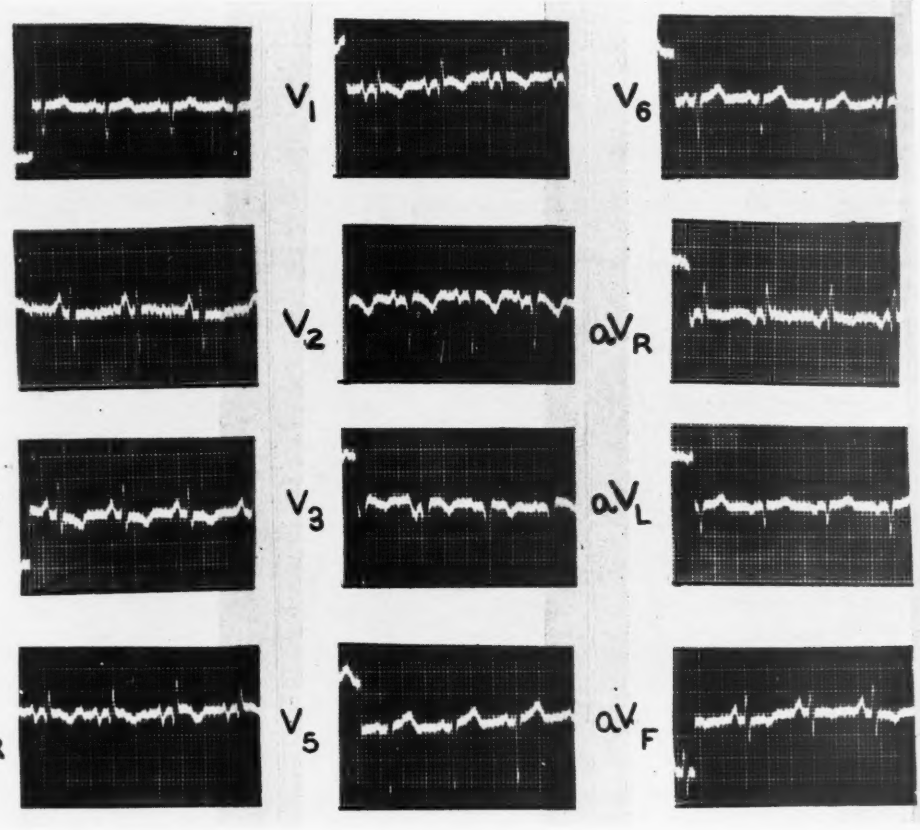

FIG. 5.—Electrocardiogram of Patient 528 is an example of the first pattern of right ventricular hypertrophy. The patient has cor pulmonale and was in heart failure. (See table 6 for measurements.)

corresponding to the third pattern of the criteria and as presumptive evidence of right ventricular hypertrophy. This may be the explanation of the changes observed in Case 334 (figs. 1 and 2). It is possible that this pattern described by Myers and colleagues[4] may be explained on the basis of position of the heart and need not be classified as presumptive evidence of right ventricular hypertrophy if leads to the right of V_{4R} are recorded.

less than 0.1 second were observed. One of these was found in the first (Patient 499), two in the second (Patients 423 and 496), and four in the third group (Patients 487, 490, 496, and 529). A point of interest is the observation that in Patient 496 the rsR′ complex was still present after the second catheterization when the pulmonary artery mean pressure had dropped from

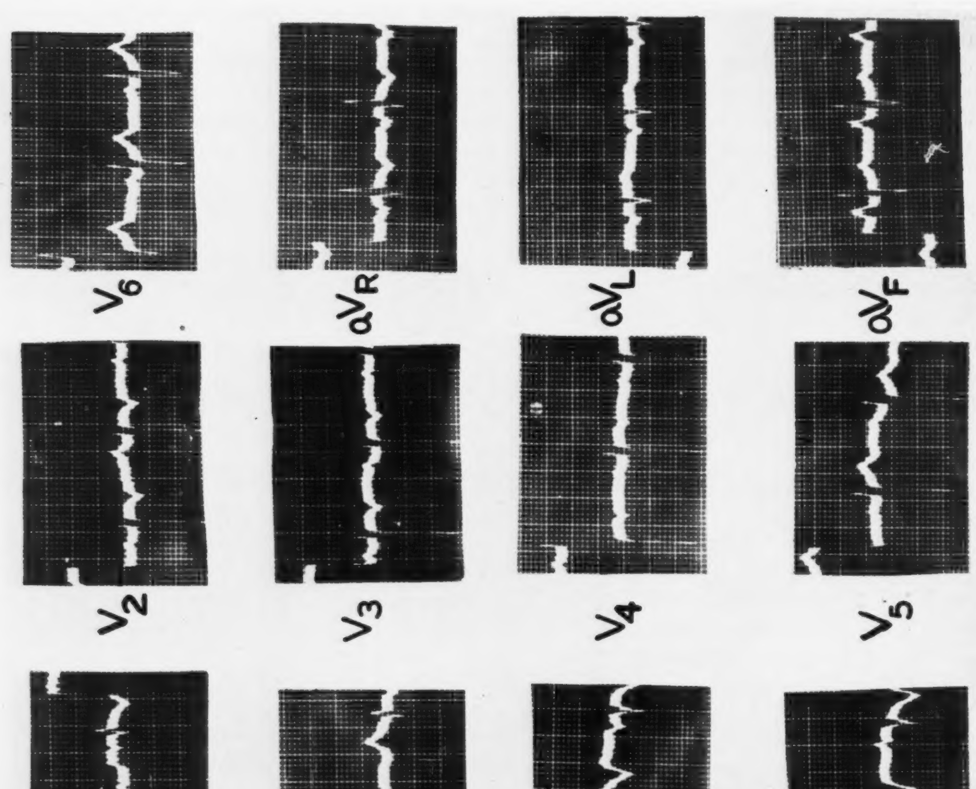

FIG. 6.—Electrocardiogram of Patient 528 made after recovery from heart failure. Note the shift of the tall R wave and large R/S ratio from V_1 to V_{5R}. (See text for discussion and table 4 for measurements.)

41 to 18 mm. mercury. This is in contrast to the transitory nature of this complex in acute cor pulmonale.

The abnormality responsible for the rsR′ pattern associated with a QRS of 0.1 second or less has never been fully clarified. Occasionally this pattern may be seen in normal hearts[10] in which instance the explanation offered by some[9, 12] is that it is due to a rotation of the heart in such a way that portions of the right heart not ordinarily explored by precordial leads are now accessible to the exploring electrode in positions V_1 and V_2. In acute cor pulmonale this configuration may be seen as a transitory phenomenon[9] and in coronary disease this pattern may also be seen, in which instance it is thought to represent incomplete right bundle branch block. The rsR′ pattern occurs in patients with right ventricular hypertrophy, but in this condition it is not known whether it represents an incomplete right bundle branch block or a phase in the development of the right ventricular hypertrophy pattern.[1, 2] Kossmann and associates[11] have studied some cases of right ventricular hypertrophy, using endocardial leads. They found that the peak of R′ in Lead V_1 occurred simultaneously with the peak of the S wave in a lead from the right ventricular cavity. Friedland and Sodi-Pallares[12] divide the tracings with the rsR′ complex into two groups, the first of which shows the electrocardiogram to be otherwise normal. The second group shows other electrocardiographic abnormalities aside from the rsR′ complex in leads V_1 and V_2. In the latter group, 90 per cent of the patients had some type of heart disease and 75 per cent showed right ventricular hypertrophy by clinical or by autopsy findings.

Although the origin of the rsR′ complex in right-sided precordial leads is still uncertain, the high incidence of this complex, especially in the group of patients with very high pulmonary arterial mean pressure, suggests some relationship of this pattern to right ventricular hypertrophy. Added weight is given this hypothesis by the changes in the electrocardiogram which occurred in Patient 490 as described above (figs. 3 and 4).

A final point to be discussed is concerned with the possible correlation between the duration of the pulmonary disease and the pulmonary arterial hypertension on the one hand and the electrocardiographic findings on the other. However, our data do not permit a satisfactory analysis of this relationship for the following reasons: (1) the insidious onset and slowly progressive nature of chronic pulmonary emphysema and of many cases of diffuse pulmonary fibrosis make it difficult to date the onset of these diseases; and (2) no data are available in these cases with regard to the duration of the hypertension. Since the development of right ventricular hypertrophy probably is related both to the degree as well as to the duration of pulmonary arterial hypertension, it is obvious that the data presented are incomplete with regard to the general problem of pulmonary arterial hypertension and electrocardiographic patterns of right ventricular hypertrophy.

Summary

1. A study of the pulmonary arterial pressure and of the electrocardiographic findings in a group of 40 patients with chronic pulmonary disease has been presented.

2. The electrocardiograms, using unipolar precordial and augmented unipolar limb leads, were analyzed for patterns identified with right ventricular hypertrophy.

3. With a single exception, none of the patients with patterns of right ventricular hypertrophy, as here defined, was observed to have a pulmonary artery mean pressure less than 30 mm. Hg at rest.

4. Of the 14 patients whose pulmonary artery mean pressure at rest exceeded 30 mm. Hg, 8 showed characteristic electrocardiographic patterns identified with right ventricular hypertrophy.

5. The rsR′ patterns in the right-sided precordial leads, of the incomplete right bundle branch block type, were found in one patient with pulmonary arterial pressure less than 15 mm. Hg; in 2 patients with pulmonary artery mean pressure between 15 and 30 mm.; and in 4 patients with pulmonary artery mean pressure above 30 mm. The significance of the high incidence of this pattern in patients with chronic pulmonary disease was discussed.

6. The absence of electrocardiographic patterns associated with right ventricular hypertrophy does not rule out the possibility of moderate or even marked pulmonary arterial hypertension.

7. Striking changes in both anatomic and electrocardiographic position of the heart were observed in patients after recovery from severe right heart failure. For this reason it is suggested that leads lateral to Lead V_{4R} as well as the usual Leads V_{3R} and V_1 through V_6 be taken in suspected cases of right ventricular hypertrophy.

ACKNOWLEDGMENT

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A Comparison of Electrokymography and Roentgenkymography in the Study of Myocardial Infarction

By Simon Dack, M.D., David H. Paley, M.D., and Marcy L. Sussman, M.D.

The authors present two cases of myocardial infarction to demonstrate that electrokymography is superior to roentgenkymography as a method for detecting localized areas of myocardial damage. This superiority is based principally on greater ease of exploration of the ventricular pulsations, clearer delineation of the kymographic curve as a result of greater magnification, and more accurate analysis of the phases of the cardiac cycle by simultaneous recording and integration with other graphic tracings.

UNTIL RECENTLY, roentgenkymography provided the only simple method of making a radiographic record of the movements of the cardiac borders during the cardiac cycle. It was found to be most useful in the diagnosis of myocardial infarction. Previous studies[1–3] by this method demonstrated that myocardial infarction produces characteristic abnormalities of left ventricular contraction, namely, (1) systolic expansion or lateral movement of the left ventricular border during systole, and (2) localized diminution or absence of pulsation. The former occurs in about one-half the cases, the latter in one-third. Sustained systolic lateral movement over the left ventricular border, with few exceptions, is pathognomonic of myocardial infarction, recent or healed, but diminution of pulsation is less specific and may occur in other types of myocardial disease.

The application of roentgenkymography to the study of myocardial disease did not become widespread for several reasons. Sufficient magnification of the ventricular movement could not easily be obtained and in the presence of impaired or diminished pulsation it was often difficult to analyze accurately the small or abnormal movements. Furthermore, since for technical reasons the x-ray exposure was limited to 1.0 to 1.5 seconds, only one or two cardiac cycles were recorded. This was a disadvantage in patients with bradycardia or cardiac arrhythmia.

Electrokymography is a method in which many of the disadvantages of roentgenkymography are minimized. In this procedure the movements of the cardiac border are recorded in the form of a graphic tracing which resembles a pulse curve. The technique of recording and analysis has been described previously.[4–8] Upward or positive movement of this curve represents lateral or outward movement of the cardiac border and downward or negative movement represents inward or medial motion of the border. By this method one can obtain magnification of the cardiac movements up to twenty times that of the roentgenkymogram. One can also record as many cycles as is consistent with safety of the fluoroscopic procedure. Another advantage of electrokymography is that by means of a four-channel recorder[8] the movements of the cardiac chambers and great vessels can be recorded simultaneously with other reference tracings, including the electrocardiogram, phonocardiogram, carotid or venous pulse tracing, and cardiac apex beat. This permits more accurate identification of the events during the cardiac cycle and more accurate comparison of the pulsation of various segments of the cardiac borders.

The clinical usefulness of this newer method of kymography will be demonstrated by comparison of electrokymography and roentgenkymography in two cases of myocardial infarction. In both of these cases the presence of infarction was not clearly demonstrated by the roentgenkymogram. Because of marked diminution in the amplitude of the left ventricular pulsation, distinct lateral movement was not clearly visualized. On the other hand, the electrokymogram recorded approximately at

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the same time presented clear evidence of infarction in the form of paradoxical or lateral movement during systole.

As a basis for comparison the appearance of the electrokymogram in a normal heart and in typical infarction of the left ventricle will be described. Figure 1 illustrates the electrokymogram of a normal adult male obtained from the middle segment of the left ventricular border simultaneously with the phonocardiogram, electrocardiogram (Lead II), and carotid pulse tracing. The film moved at a speed of 100 mm. per second; the distance between any two thin vertical lines represents 0.02 second and between any two heavy vertical lines 0.10 second. It is seen that the isometric phase of ventricular systole, marked by the onset of the first heart sound, begins 0.06 second after the beginning of the QRS complex. This is synchronous with the onset of a horizontal segment in the electrokymogram which lasts for 0.05 second (fig. 1, lines 1 to 2). A similar short horizontal segment is visible in the carotid pulse tracing about 0.025 second later, a lag which represents the transmission time of the pulse wave from the aorta to the carotid pulse and through the recording mechanism to the galvanometer.* The ejection phase is marked by a small upward or lateral movement of the kymogram synchronous with the second component of the first heart sound and with the systolic rise of the carotid pulse curve. The upward movement of the kymogram continues for 0.05 second (lines 2 to 3) and is then followed by a steep rapid downward (mesial) movement lasting for approximately 0.16 second (lines 3 to 4). It reaches its nadir at the onset of the second heart sound and dicrotic notch of the carotid pulse, which mark the closure of the aortic valve (line 4). The curve remains nearly horizontal for a period of approximately 0.13 second during the early part of diastole (lines 4 to 5). This represents the isometric phase of diastole prior to the opening of the mitral valve. The curve then rises to its presystolic level, at first rapidly (rapid inflow phase of ventricular filling, lines 5 to 6) and then less rapidly (slow inflow phase, lines 6 to 7).

* Hereafter, whenever the timing of the carotid pulse is referred to, 0.02 second has been deducted for the lag in the recording system.

It is evident that the ventricular kymographic curve in this normal case shows no movement during the isometric phase of systole. There is a short upward (lateral) movement during the early period of the ejection phase and rapid downward (medial) movement during the major part of the ejection phase. There is only minimal movement during early diastole followed by upward (lateral) movement during the remainder of diastole, which is rapid in its initial portion and less rapid in its latter portion. It is to be emphasized that there is lateral movement in early systole lasting for 0.05 second. This appears paradoxical, since it would point to the occurrence of ventricular filling instead of emptying during early systole. However, it must be remembered that the electrokymogram is not a true volumetric curve of ventricular contraction, but is a complex curve representing not only volume changes but also positional changes involving the heart during the cardiac cycle.[5, 9, 10] The latter may produce an apparent outward movement of the ventricular wall even while the ventricle as a whole is beginning to contract. In our experience and in that of others[8] the duration of this initial lateral movement in systole has not exceeded 0.06 second in normal subjects. When the lateral movement continues beyond this point, reversal of systolic pulsation as seen in myocardial infarction should be considered.

Figure 2 illustrates the typical electrokymographic findings in myocardial infarction.[8, 11] The tracing recorded over the aortic knob shows striking similarity to the carotid pulse curve, except that the ejection phase appears to start 0.03 second earlier.* The kymogram of the upper left ventricle shows the onset of downward or mesial movement, representing ventricular ejection, to be synchronous with the systolic rise of the aortic curve. In contrast, the lower left ventricular segments show sharp upward or lateral movement synchronous with the medial movement of the upper segment and with the lateral aortic movement. This represents a systolic out-thrust

* *Idem.*

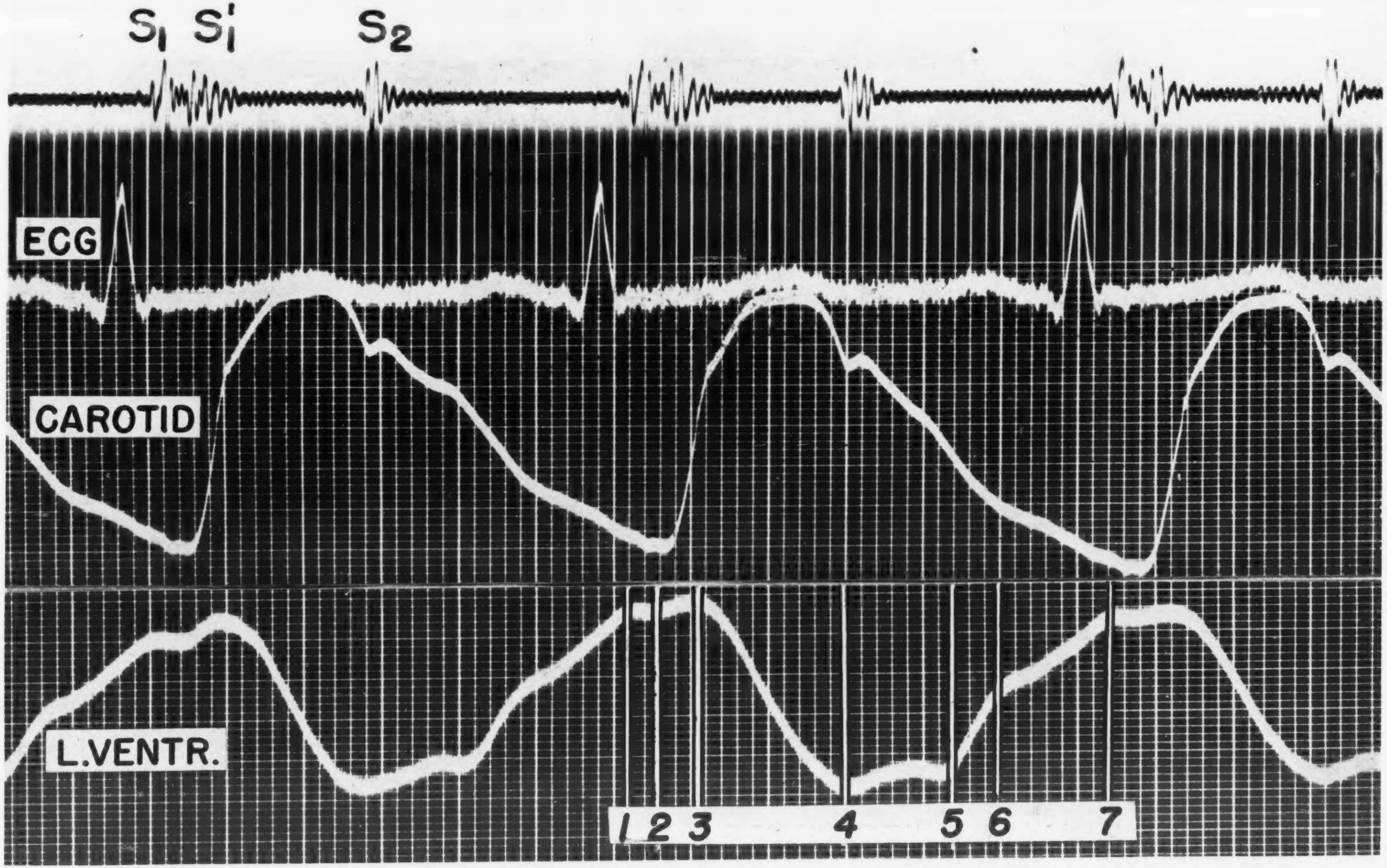

FIG. 1.—Normal electrokymogram of left ventricular border recorded simultaneously with phonocardiogram, electrocardiogram, and carotid pulse tracing. Thin vertical lines represent 0.02 second, thick lines 0.10 second.

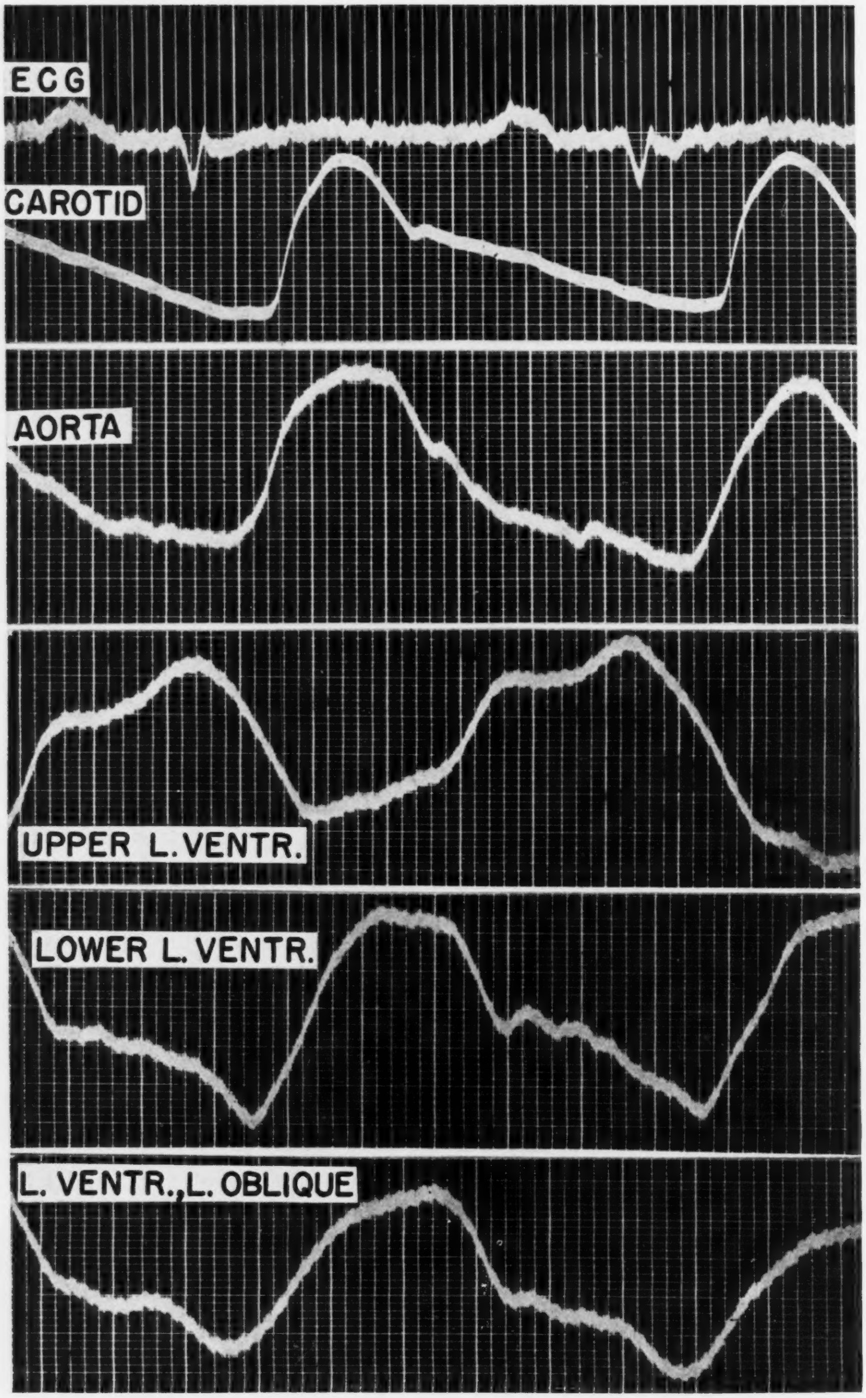

FIG. 2.—Electrokymogram of patient with infarction of left ventricle proved at autopsy, recorded with electrocardiogram and carotid pulse. There is normal contraction of upper left ventricle and sustained systolic lateral movement of lower left ventricle in posteroanterior and left oblique views (paradoxical systolic movement).

of the ventricular wall (paradoxical movement). The lateral movement continues until the onset of diastole, as marked by the dicrotic notch of the aorta. During diastole there is mesial movement of the ventricle due to the collapse of the distended segment (paradoxical movement). The typical curve of an infarcted ventricular segment thus closely resembles the normal arterial curve recorded over the aorta.

Case Reports

Case 1 (589973).

J. P., a 41 year old man, was hospitalized on Dec. 22, 1948, with the classic symptoms and clinical features of acute coronary occlusion. The electrocardiogram showed findings indicative of acute anterior wall infarction. The patient's illness ran a rather stormy clinical course suggesting extensive myocardial infarction. Several weeks after admission a visible and palpable precordial out-thrust was observed, which in the presence of a muffled and distant first sound and a systolic murmur, was suggestive of a ventricular aneurysm.

Roentgenkymography was done on March 10, 1949 (fig. 3). The tracing showed marked diminution of pulsation over the lower two-thirds of the left ventricular border. The movements of the ventricular border were so small that it was impossible to analyze them and to determine whether paradoxical movement was present.

Electrokymogram. The electrokymogram (figs. 4 and 5) recorded the same day over various segments of the cardiac border showed the following:

Aorta (fig. 4): The first heart sound begins 0.08 second after the onset of the QRS complex simultaneously with a small downward movement in the tracing of the aorta and carotid pulse, representing onset of the isometric phase of systole. Ejection in the aorta and carotid artery, represented by the sharp systolic rise of the respective curves, begins 0.15 second after the onset of the QRS at a point corresponding to the end of the first heart sound.

Mid Left Ventricle (fig. 4): The first heart sound (isometric phase) begins 0.08 second after the onset of QRS, at which time there is observed a deep downward (medial) movement of the ventricular curve which lasts for 0.06 second. This deep mesial movement during the isometric phase is unusual since the latter is generally represented by a shallow (mesial or lateral) movement or a horizontal segment (absence of movement). The ejection phase, corresponding to the middle of the first heart sound and the systolic rise of the carotid pulse, is represented on the kymographic curve by the onset of a short horizontal segment followed by a shallow downward movement. The lack of movement or shallow curve during the ejection phase is also abnormal since this phase is normally represented by a deep mesial movement (contraction of the ventricle). Ventricular filling is normal and is recorded as a sharp upward (lateral) movement beginning synchronously with the second heart sound and the dicrotic notch of the carotid pulse.

Lower Left Ventricle (fig. 5): The first heart sound begins 0.08 second after the QRS. The onset of rapid downward (medial) movement in the kymogram actually precedes the first heart sound by 0.02 second. The isometric phase of the left ventricle is thus again represented by a deep mesial movement, as was seen in the mid left ventricle. The ejection phase begins as a short upward (lateral) movement lasting 0.08 second and reaching a peak synchronously with the peak of the carotid pulse. This is followed by a second downward (medial) movement which ends at the onset of the second heart sound and dicrotic notch. These findings represent a partial reversal of ventricular pulsation with systolic expansion in the early phase of systole and delayed ventricular contraction.

Apex of Left Ventricle (fig. 5): This segment shows similar findings to those observed over the lower left ventricle. The isometric phase is represented by a shallow mesial movement beginning at the onset of the first heart sound. The ejection phase begins synchronously with the second component of the first heart sound. During ejection the kymogram shows upward (lateral) movement which reaches its peak synchronously with the peak of the carotid pulse. This is followed by delayed mesial movement which occupies the remainder of systole. Thus, in this segment, too, there is paradoxical lateral motion in early systole and delayed mesial systolic movement.

Case 2 (579924).

R. P., a 48 year old Negro, was hospitalized because of severe progressive congestive heart failure of six months' duration, manifested by marked generalized cardiac enlargement, pulmonary congestion, pleural effusion, and enlargement of the liver. The blood pressure ranged constantly between 120/90 and 130/100. The cause of the heart failure was not clear. There was no history suggesting valvular disease or acute coronary occlusion prior to the onset of the heart failure. Although only mild diastolic hypertension was present and the systolic pressure was never observed to be elevated, it was believed that the cardiac enlargement and heart failure were attributable to antecedent arterial hypertension and subsequent myocardial infarction.

The teleoroentgenogram showed marked enlargement of the heart particularly to the left. The electrocardiogram revealed the pattern of left ventricular hypertrophy and myocardial damage, but there were no findings suggestive of myocardial infarction in the extremity leads or multiple precordial leads. The roentgenkymogram (fig. 6) disclosed

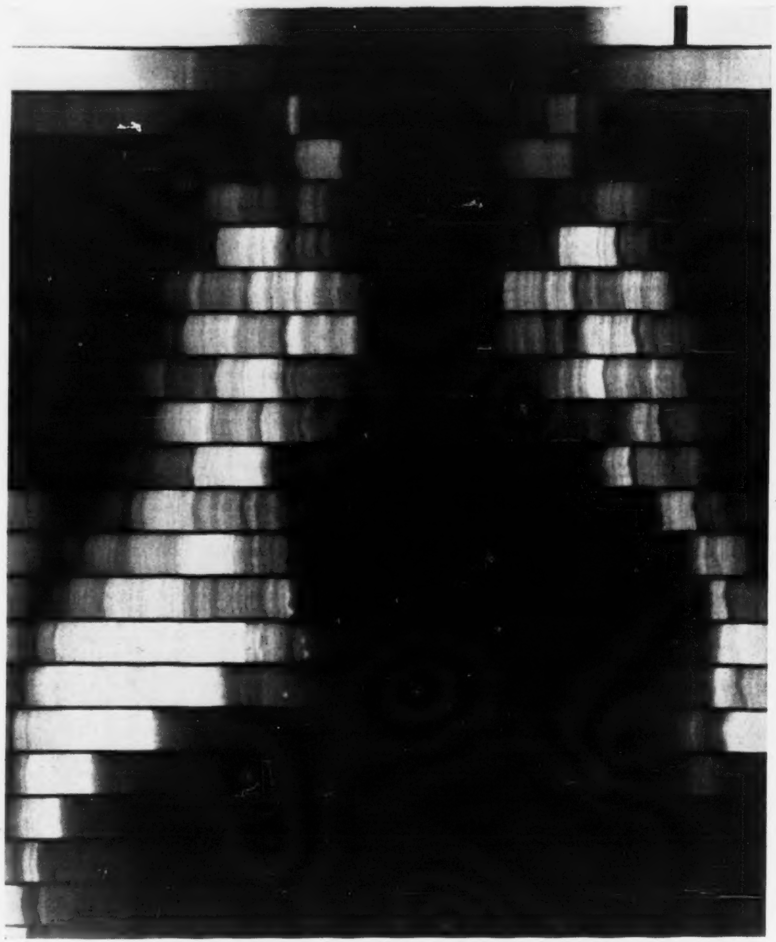

FIG. 3.—Case 1. Roentgenkymogram shows marked diminution of pulsation over lower two thirds of left ventricular border.

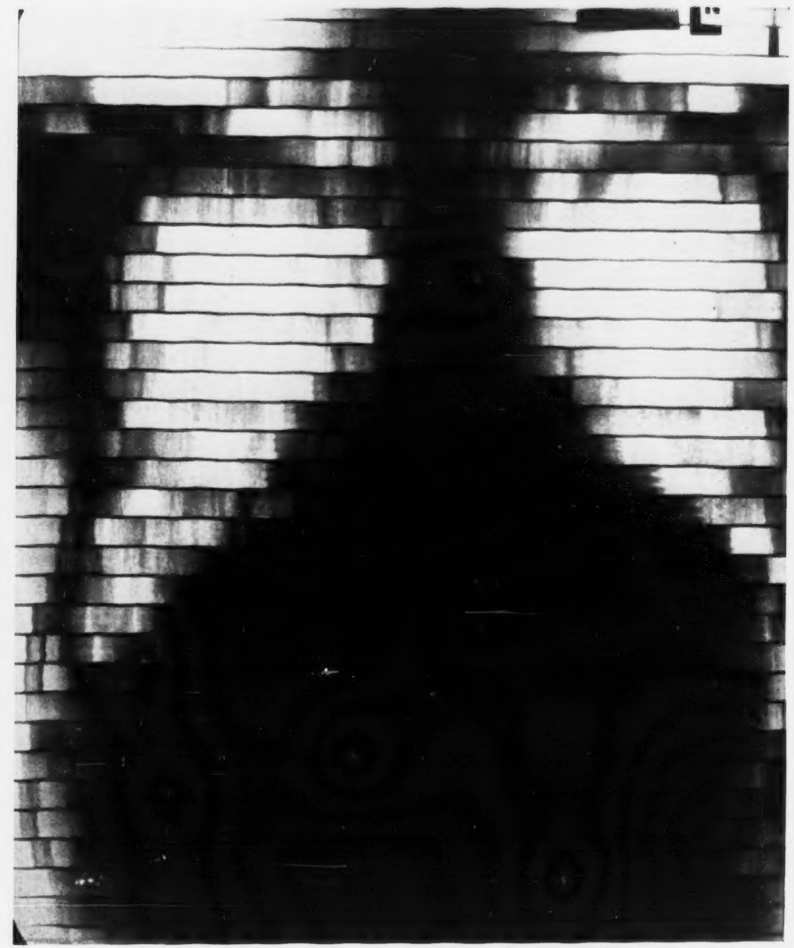

FIG. 6.—Case 2. Roentgenkymogram shows left ventricular enlargement with marked diminution of pulsation over lower half of left ventricular border.

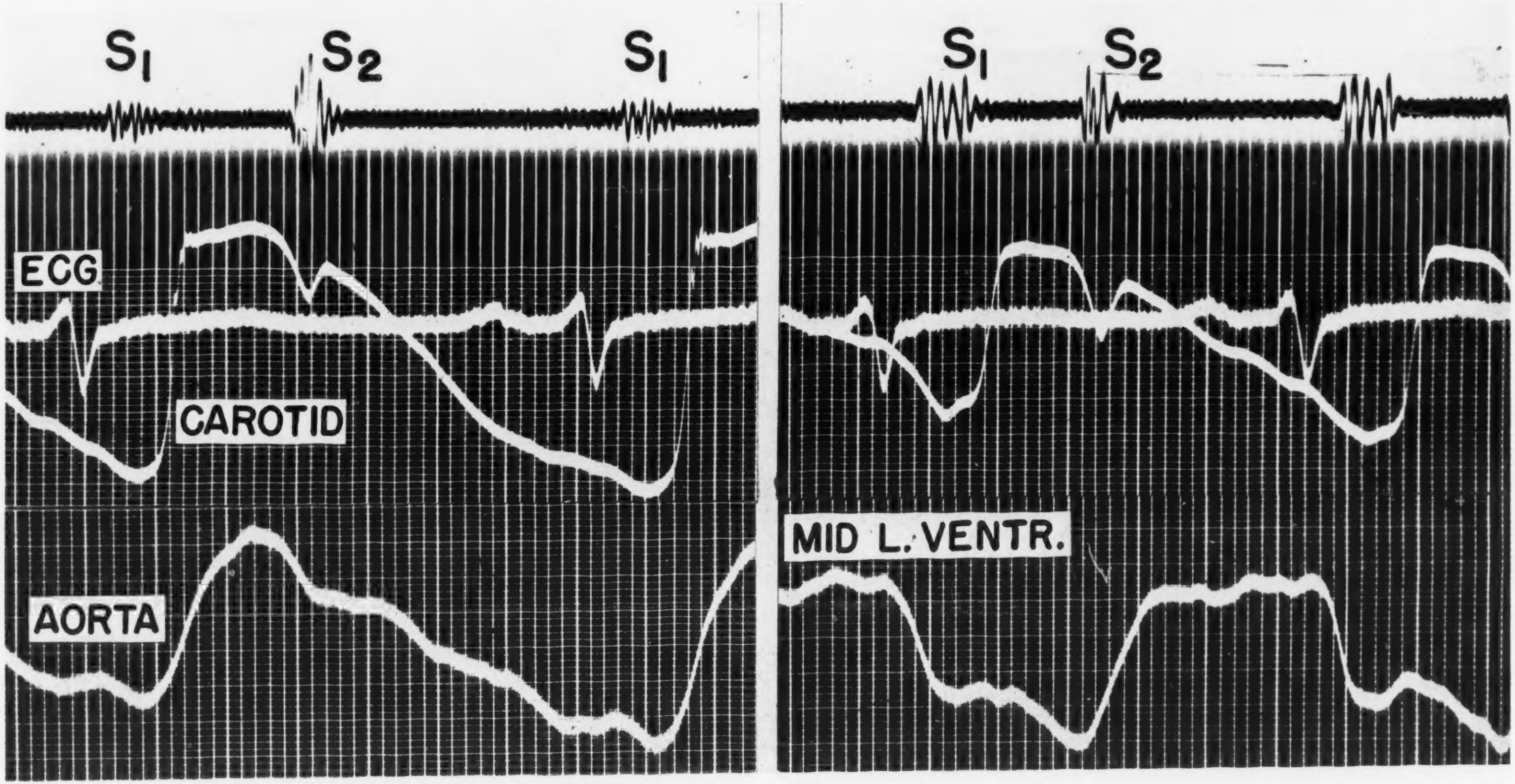

FIG. 4.—Case 1. Electrokymogram of aorta and mid left ventricle demonstrating abnormal mesial movement during isometric phase and diminished mesial movement in ejection phase.

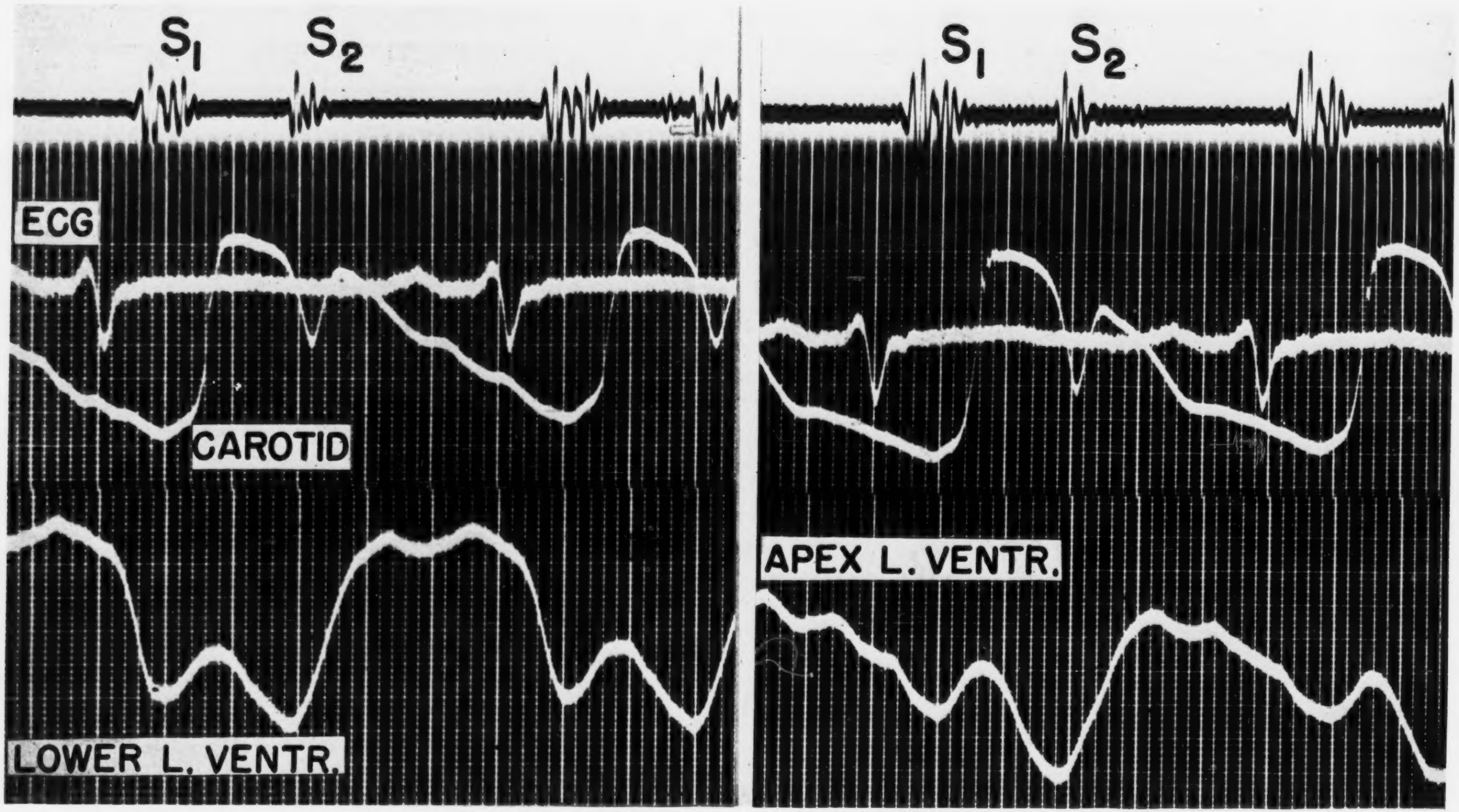

FIG. 5.—Case 1. Electrokymogram of lower left ventricle and apex showing partial reversal of ventricular pulsation with abnormal lateral movement in early systole, indicative of myocardial infarction.

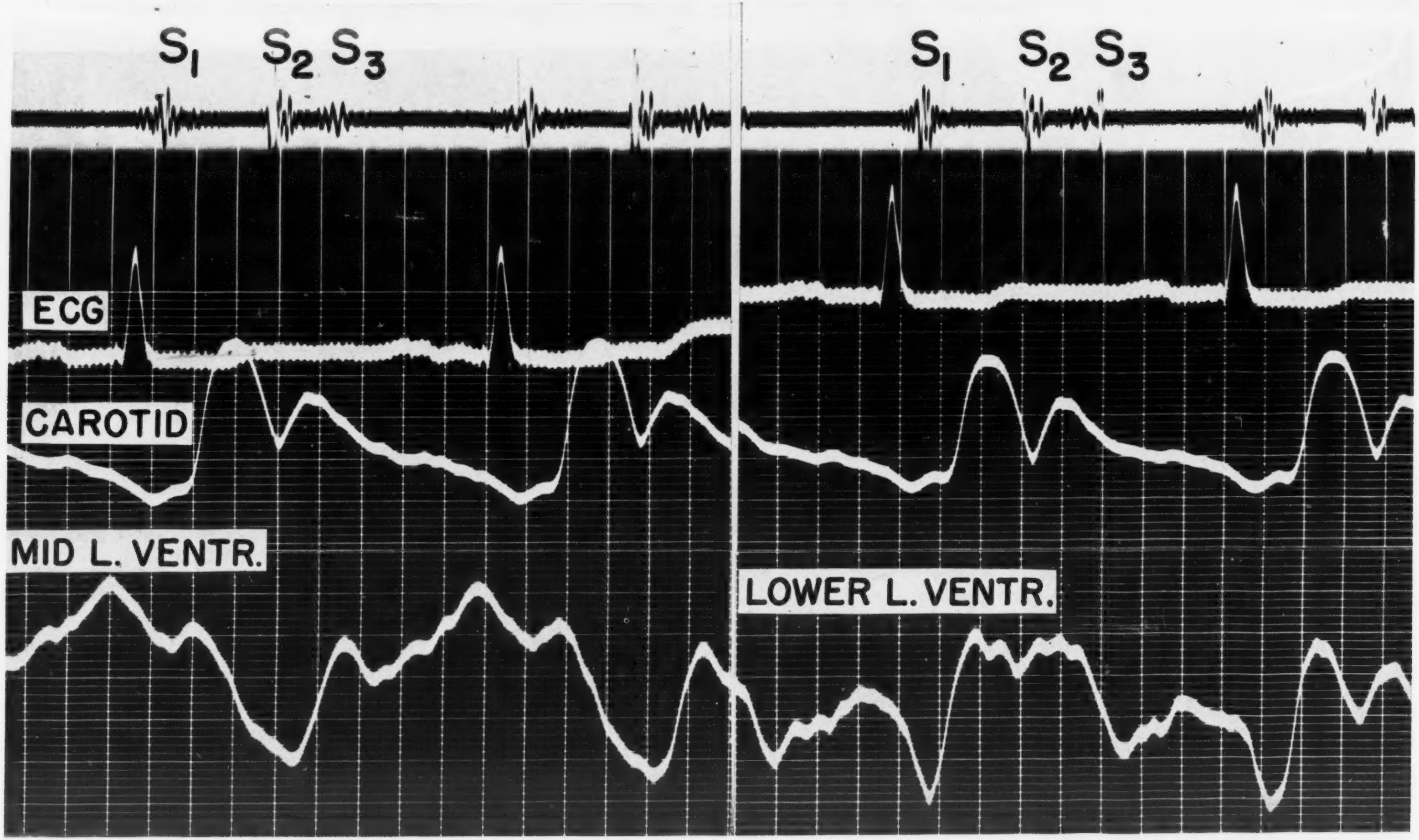

FIG. 7.—Case 2. Electrokymogram of mid left ventricle within normal range except for large auricular component in presystole. Over lower left ventricle there is abnormal deep mesial movement in isometric phase and lateral movement during ejection phase, characteristic of myocardial infarction.

marked localized diminution of pulsation over the lower half of the left ventricular border in the posteroanterior and left oblique views. This was interpreted as evidence of severe myocardial disease but in the presence of a very large heart it was not considered pathognomonic of myocardial infarction.

Electrokymogram. The electrokymogram (fig. 7) showed the following:

Mid Left Ventricle: The first heart sound begins 0.06 second after the onset of QRS. At this point the kymogram shows a small downward movement, representing the isometric phase. This is preceded by a more prominent upward (lateral) movement and peak, probably produced by auricular contraction. The ejection phase, represented by a small initial upward (lateral) movement and a prominent downward (mesial) movement, begins toward the end of the first sound, 0.14 second after the QRS. The medial movement continues even after the second heart sound and dicrotic notch of the carotid pulse, and its terminal portion extends into the isometric phase of diastole. The peak of the carotid pulse occurs at about the middle of the mesial systolic movement. The small lateral movement at the onset of the ejection phase measures only 0.04 second. This apparent paradoxical movement is not unusual since similar lateral movement measuring up to 0.06 second has been recorded in normal individuals. The above findings in our experience are essentially normal.

Lower Left Ventricle: The first heart sound begins 0.07 second after the onset of QRS. At this instant the kymogram shows a deep downward (mesial) movement lasting 0.06 second, which represents the isometric phase of systole. At 0.13 second after the onset of QRS, corresponding to the end of the first sound, the ejection phase of the ventricle begins with a sharp lateral movement which continues for 0.10 second until the peak of the carotid pulse is reached. This represents a reversal of pulsation with systolic expansion in early systole. There is only a very small mesial movement in late systole. The diastolic phase is characterized by a normal early upward (lateral) movement, but after the third heart sound there is mesial movement, which is again a reversal from the normal configuration.

It is of interest that when the patient was readmitted to the hospital several months later a second roentgenkymogram also demonstrated typical localized systolic expansion of the left ventricle.

Discussion

In our opinion the diagnosis of antecedent myocardial infarction can be made from the observation of localized systolic expansion of the left ventricle in the electrokymogram or roentgenkymogram.[2, 3, 8, 11, 12] Such paradoxical movement is represented kymographically by lateral movement during systole, which may begin during the isometric phase or at the onset of the ejection phase, synchronously with the first heart sound and with the lateral systolic movement of the aorta and carotid artery. Although such paradoxical movement usually is well visualized in the roentgenkymogram it is more striking and distinct when recorded by the electrokymogram. This is particularly true when the paradoxical movement is small, as demonstrated in the two cases reported above. In such instances the abnormal ventricular pulsation is better detected with the magnification afforded by the electrokymogram and with the aid of the other reference tracings.

Our past studies[2, 3, 13] in hundreds of cases of myocardial infarction studied kymographically have shown that the abnormal ventricular contraction usually is limited to the lower segment and apex of the left ventricle, both in the posteroanterior and left oblique views. However, despite the conclusions reached by others,[12] we found that no correlation can be made between the site of the abnormal ventricular movement and the localization of the myocardial infarct determined electrocardiographically or at autopsy. We have frequently observed cases of posterior or basal infarction in which paradoxical movement was visible over the lower left ventricular border in the posteroanterior view.[3, 13] Therefore, exact localization of the site of infarction should not be asserted from the kymographic findings. Nevertheless the extent of distribution of such lateral movement over the left ventricular border may be a guide to the size of the infarct or scar.

Analysis of the typical electrokymogram in myocardial infarction shows that the lateral movement which begins in the isometric phase or at the onset of the ejection phase is generally sustained for the entire duration of systole (fig. 2). It reaches a peak synchronously with the peak of the aortic kymogram or carotid pulse curve and continues until the closure of the semilunar valves (dicrotic notch). It is then followed by a paradoxical mesial movement during diastole. The paradoxical movement during systole may not be complete. Instead of a sustained lateral movement throughout

systole there may be only a transient reversal of the direction of ventricular movement either in early or late systole. In the former type, which is more common, a short lateral movement occurs in the early phase of systolic ejection and is followed by a delayed but normal mesial movement. In the second type, normal early mesial movement is cut short by abnormal lateral movement during the later part of systolic ejection. The two cases discussed in this report fall into the first group of partial or incomplete systolic expansion. In Case 1 (figs. 4 and 5) it was demonstrated that lateral movement continued for 0.08 second after the onset of ejection and was succeeded by the delayed mesial movement of ventricular contraction. Similarly, in Case 2 (fig. 7) there was an early sharp paradoxical lateral movement lasting 0.10 second but the succeeding mesial movement was more shallow than in Case 1.

It is of interest that paradoxical ventricular movement occurs not only during systole but also during diastole. Normally the ventricular kymographic curve shows upward (lateral) movement following the isometric phase of diastole. This portion of the tracing is steep in the early phase and shallow in the later phase, corresponding to rapid and slow ventricular filling, respectively (fig. 1). However, in the presence of paradoxical movement in systole when the kymographic tracing is sustained in the lateral position until the end of systole, diastole is represented by rapid downward (medial) movement. This paradoxical medial movement may continue during the entire diastole (fig. 2) or it may occupy only the initial phase of diastole (fig. 7). These findings suggest that both contraction and filling are abnormal in the impaired ventricular segment. The lateral movement during systole represents a systolic out-thrust of the weakened ventricular wall when intraventricular pressure is raised. The abnormal medial movement in diastole represents virtually a collapse of the involved wall during early diastole which may persist until the succeeding systole or may be transient and be followed by varying degrees of ventricular filling.[14, 15]

Paradoxical ventricular movement in early systole must be differentiated from the short early lateral movement which may occur during the isometric or initial ejection phase in normal hearts. For this reason accurate determination of the onset of the isometric and ejection phases is important. The apparatus and method of analysis used by us are particularly well suited for this purpose, since the ventricular movement is recorded simultaneously with the electrocardiogram, heart sounds, and carotid pulse, which furnish a variety of reference points in the cardiac cycle. The onset of the isometric phase in the electrokymogram is fairly easy to determine, since it is generally synchronous with the onset of the first heart sound. In the same individual the onset of the first sound has a fixed time relation to the beginning of the QRS complex, so that the former can be determined with fair accuracy even when the base line is distorted by artefacts.

By contrast there is considerable difficulty in accurately localizing the initial point of the ejection phase (or termination of isometric phase). Various methods have been employed, such as correlation with (1) the electrocardiogram,[6] which we have found to be inaccurate; (2) the second component of the first heart sound,[7] which is certainly not distinct in every case and might lead to gross error; (3) the onset of ejection in the aorta and carotid artery,[4, 5] which usually begins as a sharp upstroke on the tracing. With the latter method one must take into account a lag of 0.01 second in transmission to the aortic knob, an additional lag of 0.01 second in transmission to the carotid artery, and 0.01 second in the conduction system of the recording mechanism. This makes a total of approximately 0.02 to 0.03 second lag between the ventricular kymogram and the carotid pulse tracing.

The usual duration of the isometric phase as determined by physiologic methods is stated to be 0.04 to 0.06 second.[16, 17] In general, this has conformed to the values obtained electrokymographically. Several normal variations of the configuration of the isometric phase of the left ventricular kymogram have been observed: (1) The segment may remain horizontal, indicating absence of ventricular movement; this

is seen in a small percentage of the cases. (2) The segment may move upward (laterally) for an interval not exceeding 0.05 to 0.06 second. (3) The segment may show a shallow downward (medial) movement before the sharp medial movement of ejection. The latter is probably the most common configuration. A short momentary lateral movement may also occur at the onset of the ejection phase as well as during the isometric phase. The duration of such lateral motion at the onset of ejection has been estimated to be 0.06 second or less.[8] Lateral motion in systole beyond this interval should therefore be considered paradoxical.

The normal lateral movement during the isometric and early ejection phases has been attributed in part to the contraction of the interventricular septum which precedes contraction of the free walls. This may result in shortening of the vertical axis of the heart and a transient lateral bulge of the free wall.[18–20]

Finally, it must again be emphasized that the kymographic tracings cannot be accepted as representative of simple volumetric changes within the great vessels or ventricles.[5, 15] Positional changes produced by torsion, traction, or pendulum movement of the heart as a whole are important factors in the complex curve recorded by the electrokymogram.

Summary

1. A description is presented of a method of recording and analysis of the electrokymogram, utilizing simultaneous recording of the electrocardiogram, heart sounds, and carotid pulse tracings as reference points to identify the events in the cardiac cycle.

2. The electrokymogram of the left ventricle in the normal heart and in the presence of myocardial infarction is described.

3. The electrokymogram in myocardial infarction often discloses paradoxical (lateral) movement of the left ventricular border in systole and medial movement in diastole.

4. The clinical value of electrokymography is emphasized by the findings in two cases of myocardial infarction, in which the electrokymogram clearly demonstrated these characteristic abnormalities which the roentgenkymogram failed to disclose.

5. The normal variations in the curves of the isometric and ejection phases are described to minimize or prevent an erroneous diagnosis of abnormal ventricular movement.

6. It is emphasized that the electrokymogram represents a combination of volumetric and complex positional changes.

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Studies of Plasma Quinidine Content

I. Relation to Single Dose Administration by Three Routes

By Richard W. Kalmansohn, M.D., and John J. Sampson, M.D.

The plasma quinidine curves obtained by the oral and intramuscular routes of administration of 0.6 Gm. quinidine sulfate and 0.65 Gm. quinidine lactate, respectively, were generally similar. Maximal concentration, averaging 3.2 mg. per liter in the former group occurred from one-half hour to four hours after administration, and in the latter averaged 2.6 mg. per liter in one to three hours. Significant quantity of quinidine remained at eight hours, and small amounts at twenty-four hours. Rectal administration of 0.6 Gm. quinidine sulfate resulted in lower concentrations, the maximum averaging 0.89 mg. per liter. The chief value of intramuscular quinidine therapy appears to be the avoidance of gastrointestinal irritation, but hypotensive reactions were relatively frequent in the small series of patients studied.

SEVERAL groups of workers have reported the plasma quinidine concentrations after the oral administration of single doses of quinidine sulfate.[1-4] In the present study, quinidine sulfate was given orally and rectally and quinidine lactate intramuscularly, and the pattern of quinidine concentration was determined at various times after administration.

The plasma quinidine content was determined by the fluorometric method described by Brodie and Udenfriend in 1943.[5] The procedure consists of adding a fixed volume of metaphosphoric acid to a diluted plasma specimen to obtain a protein-free filtrate, and then of determining the concentration of quinidine in the filtrate by means of a photofluorometer.

The patients (table 1) were chosen at random, but with care to exclude anyone with gastrointestinal or urinary tract disturbances. Plasma samples were obtained prior to the administration of the quinidine and at regular intervals thereafter, usually according to the following schedule: at fifteen, thirty, and sixty minutes, and at two, four, eight, twelve, and twenty-four hours.

The observations in 6 patients using single oral doses of 0.6 Gm. of quinidine sulfate (fig. 1) showed maximum plasma quinidine contents varying from 2.9 to 3.7 mg. per liter with an average content of 3.2 mg.; these peak concentrations occurred from one-half to four and one-quarter hours after administration of the drug, or in an average time of two and one-quarter hours. The fall in plasma content of quinidine (table 2) occurred at about the following rates: 55 to 96 per cent of the maximum concentration remained in four hours, 42 to 73 per cent remained in eight hours, and 0 to 22 per cent was still present in twenty-four hours.

The above findings are approximately the same as those observed by other investigators. Wegria and Boyle[1] gave 4 patients 0.8 Gm. and 2 patients 0.6 Gm. of quinidine sulfate orally and observed maximum plasma concentrations ranging from approximately 2.0 to 3.0 mg. per liter in from one to four hours. Delevett and Poindexter[2] administered 1.0 Gm. of quinidine to 20 patients and noted maximum concentrations varying from 1.48 to 4.32 mg. per liter in from three-quarters to four hours. Hiatt[3] gave 10.0 mg. of quinidine per kilogram of body weight (approximately 0.70 Gm. to a patient weighing 150 pounds) and recorded maximum concentrations of from 2.0 to 3.0 mg. per liter in two to three hours in several patients. Linenthal, Ulick, and Patterson[4] noted average maximum quinidine concentrations of 2.0 mg. per liter occurring in from one to three hours after doses of 0.6 Gm. of quinidine were administered. Though the quinidine

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TABLE 1.—*Plasma Quinidine Concentrations in Subjects with Sinus Rhythm after the Administration of Single Doses by Oral, Rectal, or Intramuscular Routes*

Case	Sex	Age (years)	Height (feet-inches)	Weight (pounds)	Dose (gram)	Maximum Level (mg./Liter)	Time Required for Maximum Concentration to be Reached after Administration of Quinidine (hours)	Number of Hours Quinidine Still Detected in Plasma
1-MB	M	65			0.6 orally	3.1	2	24
2-AD	M	43	5-5	145	0.6 orally	2.9	½	13
3-GG	F	26	5-8	125	0.6 orally	3.4	4½	18
4-RS	M	64	5-6	125	0.6 orally	3.7	1½	24
5-MM	M	63	5-7	170	0.6 orally	3.0	1½	24
6-AY	F	59	5-2	155	0.6 orally	3.36	3½	24
7-EG	M	73	5-5	132	0.6 rectally	1.1	2	8
8-KC	F	66	5-0	155	0.6 rectally	0.51	3½	11
9-WR	M	65	5-6	140	0.6 rectally	0.75	6	12
10-MG	M	78	5-6½	128	0.6 rectally	1.19	1½	12
11-ST	F	59	5-0	95	0.13 IM	0.43	¾	6½
12-JM	F	70	5-1½	135	0.13 IM	0.85	3½	11
13-RH	F	67	5-1	88	0.65 IM	1.76	2½	24
27-JG	M	27	5-6	106	0.65 IM	3.45	1	24
28-MA	F	59	5-4	179	0.65 IM	3.20	2⅔	24
33-KM	M	51			0.65 IM	2.34	3	24

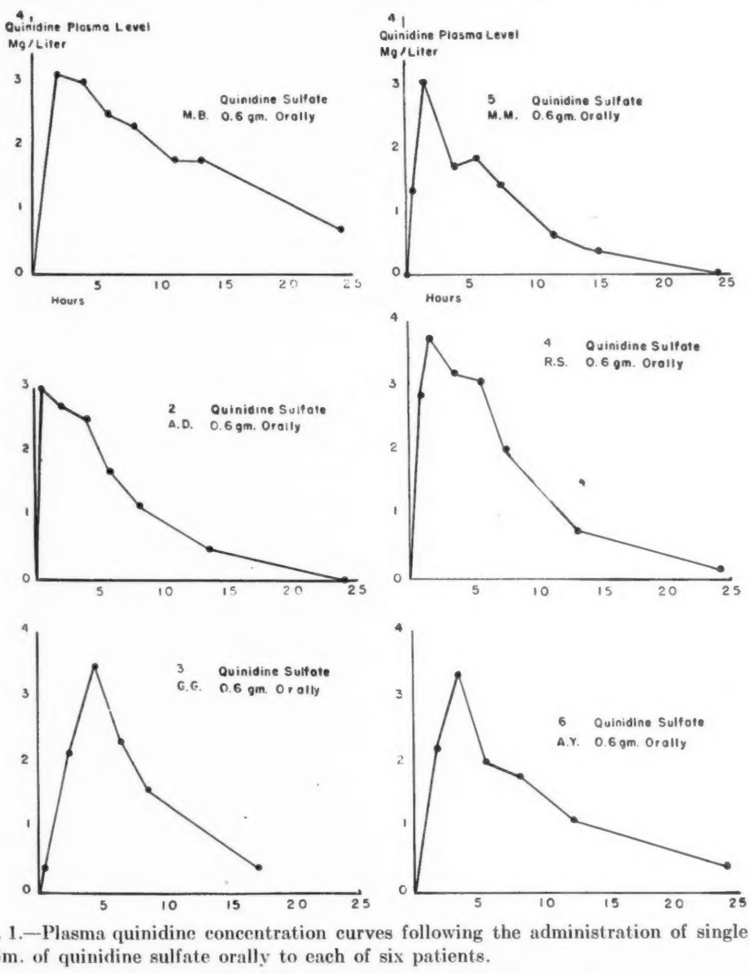

FIG. 1.—Plasma quinidine concentration curves following the administration of single doses of 0.60 Gm. of quinidine sulfate orally to each of six patients.

concentrations fluctuated among individuals, the average concentrations did not show much variation when dosages of from 0.6 to 1.0 Gm. were given in the above groups of cases.

Six patients were given quinidine lactate,* intramuscularly. Five of these are illustrated in figure 2. Of this group, 2 patients received 0.13 Gm. and showed maximum plasma contents of 0.85 and 0.43 mg. per liter in three and three-quarters and three-quarters hours, respectively. Four patients received 0.65 Gm. each and the maximum plasma contents varied from 1.76 to 3.45 mg. per liter with an average of 2.68 milligrams. The peaks occurred in an average of two and one-third hours with a range of from one to three hours; this is similar to the peak concentrations obtained in those patients who received quinidine orally. The percentage fall from maximum concentrations (table 2) was less than for the orally administered quinidine; 71 to 94 per cent remained at four hours, 45 to 83 per cent at eight, and 10 to 28 per cent at twenty-four hours. Assuming that these figures are significant, it is possible that the delay in excretion could be due to fixation of quinidine by skeletal muscle, which has been demonstrated by Wegria and Boyle[1] to fix about one-third to one-half the quantity of quinidine fixed by cardiac muscle. There was more variation of the maximum quinidine plasma concentrations among those receiving the drug intramuscularly than among those receiving it orally.

TABLE 2.—*Fall in Concentration of Plasma Quinidine after Administration of the Drug by Three Different Routes Expressed in Approximate Percentage of the Maximum Levels Reached at Various Times*

Case	Max. Conc. Reached in Following Hours	4 Hours After Administration (Per Cent)	8 Hours After Administration (Per Cent)	24 Hours After Administration (Per Cent)
Intramuscularly				
13-RH	$2\frac{1}{2}$	71	45	10
27-JG	1	94	64	20
28-MA	$2\frac{2}{3}$	93	75	25
33-KM	3	83	83	28
Orally				
1-MB	2	96	73	22
2-AD	$\frac{1}{2}$	85	42	0.0
3-GG	$4\frac{1}{2}$	*	47	9.0
4-RS	$1\frac{1}{2}$	87	55	4.0
5-MM	$1\frac{1}{2}$	55	45	2.7
6-AY	$3\frac{1}{2}$	—	52	12.0
Rectally				
7-EG	2	92	61	0.0
8-KC	$3\frac{1}{2}$	—	66	0.0
9-WR	6	*	80	0.0
10-MG	$1\frac{1}{2}$	67	40	0.0

* Maximum concentrations occurred after the four-hour determination.

In 4 patients who were given 0.6 Gm. of quinidine sulfate rectally (fig. 3), the maximum plasma quinidine contents varied from 0.51 to 1.19 mg. per liter, an average of 0.89 mg., with peaks at one and one-half to six hours in an average time of three and one-quarter hours. About 40 to 80 per cent of the maximum concentration was present in eight hours, only a trace remained at twelve hours, and none was detected at twenty-four hours after the time of administration (table 2).

There was no consistent correlation between the weights of patients and the plasma quinidine concentrations.

Summary and Conclusions

1. The plasma quinidine concentrations observed when the drug was given by three routes, orally, intramuscularly, and rectally, were compared. The maximum concentrations following the administration by the three routes of approximately 0.60 Gm. of quinidine averaged, respectively, 3.2, 2.68, and 0.89 mg. per liter in an average time of two and one-quarter, two and one-third, and three and one-quarter hours.

2. The intramuscular route, resulting in approximately the same plasma concentration curves as when the drug is given by the oral route, would seem to be valuable chiefly when quinidine cannot be given orally because of certain patients' intolerance to the oral administration as evidenced by nausea or diarrhea and

*Quinidine lactate was generously supplied by Eli Lilly and Co.

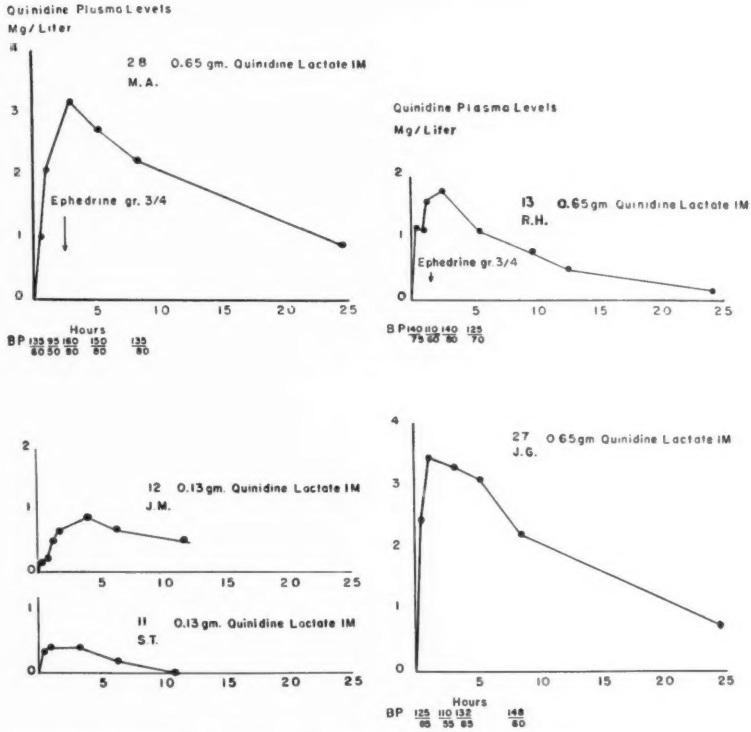

FIG. 2.—Plasma quinidine concentration curves following the administration of single doses of quinidine lactate, 0.6 or 0.13 Gm. intramuscularly, to each of five patients.

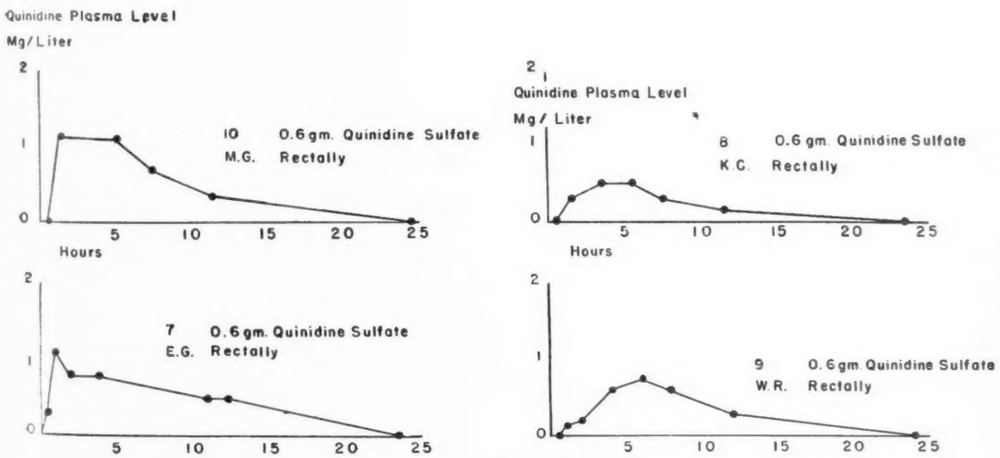

FIG. 3.—Plasma quinidine concentration curves following the administration of 0.60 Gm. of quinidine sulfate rectally to each of four patients.

when nausea and vomiting preclude any oral medication. Quinidine can be administered rectally, but dosages probably two to three times those used orally may be necessary to obtain equivalent plasma concentrations.

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Studies of Plasma Quinidine Content

II. Relation to Toxic Manifestations and Therapeutic Effect

By Richard W. Kalmansohn, M.D., and John J. Sampson, M.D.

The gastrointestinal symptoms of quinidine toxicity occurred without relation to plasma concentration, suggesting that most examples are due to individual local gastrointestinal sensitivity and some, associated with giddiness, occur only at higher levels and may be due to nervous system effects. Tinnitus, visual disturbances and marked hypotension generally occurred at relatively high plasma quinidine concentrations. It is suggested that hypotension is due to a nervous system effect rather than to myocardial incompetence, but nonetheless warrants cessation of administration.

MANY forms of quinidine toxicity have been noted in the past. Certain of these toxic symptoms and signs have been assumed to be idiosyncrasies and sensitizations[1, 2] and others to be related to the amount of medication given. One of the purposes of this study is to consider whether the symptoms and signs are related to quinidine plasma concentrations or to idiosyncrasies and sensitizations or possibly to both factors.

It has likewise been considered worth while to record case studies in which the plasma quinidine concentrations have been determined in patients approximately at the time that auricular fibrillation has been converted to sinus rhythm. In addition the pattern of quinidine blood levels will be demonstrated in patients who received steadily increasing doses of quinidine.

The fluorometric method for measuring the plasma concentrations was described by Brodie and Udenfriend.[3]

Toxicity

The plasma quinidine contents at which various toxic symptoms and signs were observed are illustrated in table 1. In six out of fourteen instances among 12 patients in whom quinidine was administered orally in an attempt to convert auricular fibrillation to sinus rhythm, toxic symptoms and signs were observed. These symptoms and signs fell into three groups.

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The gastrointestinal symptoms were nausea, vomiting, and abdominal cramps with diarrhea. The amounts of quinidine in the plasma at the time when these symptoms occurred varied widely, including very low concentrations. This probably indicates a local rather than other visceral or nervous system influence.

The second group of symptoms can be classed as labyrinthine, and include tinnitus and deafness. These occurred early in therapy, suggesting unusual susceptibility to cinchonism, but they probably can occur in almost all patients if the dosage of quinidine is great enough.

Another series of symptoms can be classified under probable central nervous system effects. These include diplopia, scotomata or colored visual aura, fall in blood pressure, and headache. Giddiness, although suggesting a cerebral effect, may possibly be referred to any of the three classified groups. Although a specific toxic effect on the myocardium has been claimed as the cause of circulatory collapse, the central nervous system origin of precipitant hypotension is suggested in past experience in patients given quinidine intravenously. Then the blood pressure fell concurrently with a depression of the respiratory rate and with diplopia, without change in cardiac rhythm. Such signs and symptoms occurred generally at high concentrations although variations from 0.65 to 14.5 mg. per liter were noted. Since these symptoms are uncommon and do not regularly occur even at high plasma concentrations of quinidine, it is likely that they represent an individual hypersensitivity of some patients to quinidine.

A marked fall in blood pressure is believed to be the most serious of the toxic reactions since it implies impending circulatory failure. Ferrer and co-workers[4] report frequent instances of hypotension with diminished peripheral resistance following oral dosage of 0.8 Gm. of quinidine. The occurrence of peripheral autonomic nervous or local vasodilator influences is suggested by this work and cannot be excluded as a possible mechanism for the hypotension following the administration of quinidine. Hiatt,[5] experimenting with dogs, gathered evidence indicating that the fall in blood pressure following the administration of quinine or quinidine was due in part, at least, to peripheral vasodilatation.

It is apparent that the symptoms in all of these three groups occurred over a wide range of plasma quinidine concentrations. This represents individual susceptibilities, and it is not possible to predict when a patient will develop specific toxic symptoms by comparing him to another patient. It may be possible to anticipate what symptoms will occur when the same patient is observed under quinidine therapy on repeated occasions although not necessarily at what phase of the treatment. Thus, one of the 13 patients treated several different times for auricular fibrillation manifested diarrhea on two occasions at plasma quinidine concentrations of 3.5 and 10.8 mg. per liter and tinnitus at 3.5 and 7.95 mg. per liter, respectively.

Little evidence of changes in electrocardiograms was noted at about the time of conversion. One patient (Case 14, *c*, table 2) showed a transient atrioventricular conduction delay with nodal rhythm and a Q-T interval of 0.54 second; on another occasion this same patient (Case 14, *b*) showed a P-R interval of 0.24. One patient (Case 15) had a P-R interval of 0.25. Another patient (Case 22) showed a Q-T interval of 0.58, a P-R interval of 0.24 second, and premature nodal beats.

An abrupt, significant fall of blood pressure was noted shortly before the maximum plasma quinidine concentrations were reached in two of four patients receiving single doses of 0.65 Gm. of quinidine lactate intramuscularly; the maximum plasma contents in these patients were 3.2 and 1.76 mg. per liter. The blood

TABLE 1.—*Plasma Quinidine Concentrations at the Onset of Certain Forms of Toxicity. (Observation of fourteen instances of one or more forms of toxicity occurring in six of twelve patients receiving quinidine therapy for auricular fibrillation.)**

Evidence of Toxicity	Plasma Quinidine Concentrations in mg./Liter					Total Cases
	0.5–1.9	2–4.9	5–7.9	8–10.9	11–15	
Gastrointestinal (Local)						
Nausea	#21	#23	#15, #25	#14, *c*		5
Vomiting		#23				1
Abdominal cramps and diarrhea	#15	#14, *b*		#14, *c*		3
Labyrinthine						
Tinnitus		#14, *b*, #25	#14, *c*		#15	3
Deafness					#15	1
Central Nervous System						
Giddiness	#25	#14, *b*	#15			3
Headache		#21	#23			2
Scotomas or colored aura		#21		#25		2
Diplopia				#25	#15	2
Fall in blood pressure			#23	#25		2
Total Cases	3	4	4	2	1	

* The number symbol (#) preceding the arabic numerals indicates the case number.

pressure fell in these two patients from 135/60 to 95/50 and from 140/75 to 110/60. The hypotension was corrected by the subcutaneous administration of 0.05 Gm. of ephedrine sulfate. Of the 13 patients studied during oral quinidine therapy, 2 (Cases 23 and 25, table 1) exhibited falls in blood pressure of 140/80 to 94/70 and 115/75 to 86/60, respectively, but greater risk owing to the effect on blood pressure than does quinidine given orally or rectally. It is felt that although no serious sequelae developed, a fall in blood pressure is one of the chief indications for discontinuing the administration of uinidine. Ventricular tachycardia as possibly heralding ventricular fibrillation has been suggested as another grave com-

TABLE 2.—*Relation of Quinidine Plasma Levels to Conversion of Auricular Fibrillation to Sinus Rhythm in Patients with Rheumatic and Coronary Arteriosclerotic Heart Disease*

Case	Sex	Age	Weight	Type Heart Disease	Duration Aur. Fib.	Total Dose in Grams	Days Needed to Convert	Plasma Level at Time of Conversion
								mg./liter
15 MF	M	38	180	RHD with aortic insufficiency	12 days	43.2	9	23.78
22 NS	M	60	160	RHD with mitral stenosis	1½ years	13.2	4	15.20
14*a* MV	F	47	180	RHD with mitral stenosis	3 days	12.5	3	14.06
14*b* MV	F	47	180	RHD with mitral stenosis	3 days	14.8	3	11.70
14c MV	F	47	180	RHD with mitral stenosis	3 days	15.2	3	10.80
31 EK	F	51	150	RHD with mitral stenosis	7 years	6.8	2½	9.0
17 MC	F	38	—	RHD with mitral stenosis	6 days	1.2	6 hours	7.48
26 EB	M	55	169	Cor. art. HD	7 years	11.2	4	9.45
32 BR	M	60	160	Cor. art. HD and hypertension	10 months	2.6	2	5.85
16 TG	F	63	149	Cor. art. HD and hypertension	1 day	4.4	1	5.67
29 JM	F	70	135	Cor. art. HD and hypertension	8 hours	0.5	6 hours	5.27
18 HN	M	62	185	Cor. art. HD	8 hours	1.7	7 hours	4.55
21 SG	F	63	183	Cor. art. HD and hypertension	18 hours	1.0	18 hours	3.30
23 EO	M	61	180	Cor. art. HD	1 year	2.6	did not convert	6.90 (peak conc.)
25 LG	M	56	170	Cor. art. HD	?	15.2	did not convert	8.10 (peak conc.)

at higher plasma quinidine concentrations, namely, 6.9 and 8.1 mg. per liter. The blood specimens were obtained from one patient (Case 23) about one hour after the blood pressure fell and from another patient (Case 25) at the time the blood pressure fell. This implies that the administration of quinidine intramuscularly, as has been suspected from previous experience with its intravenous use, carries a plication and should impel cessation of therapy.[6] Frequent blood pressure determinations should be made especially when other toxic symptoms have been manifested in order to detect abrupt depression of blood pressure.

Therapy of Auricular Fibrillation

The plasma quinidine content of 11 patients at the time of conversion of auricular fibrilla-

tion to sinus rhythm varied from 7.48 to 23.7 mg. per liter in seven instances among 5 patients with rheumatic heart disease (including three conversions in the same patient), and 3.3 to 9.45 mg. per liter in 6 patients with coronary arteriosclerotic heart disease with or without hypertension. The curves of plasma quinidine concentration and the quinidine dosage of 6 of these patients are illustrated in figure 1. Quinidine therapy was discontinued before conversion in two patients because the blood pressure fell significantly.

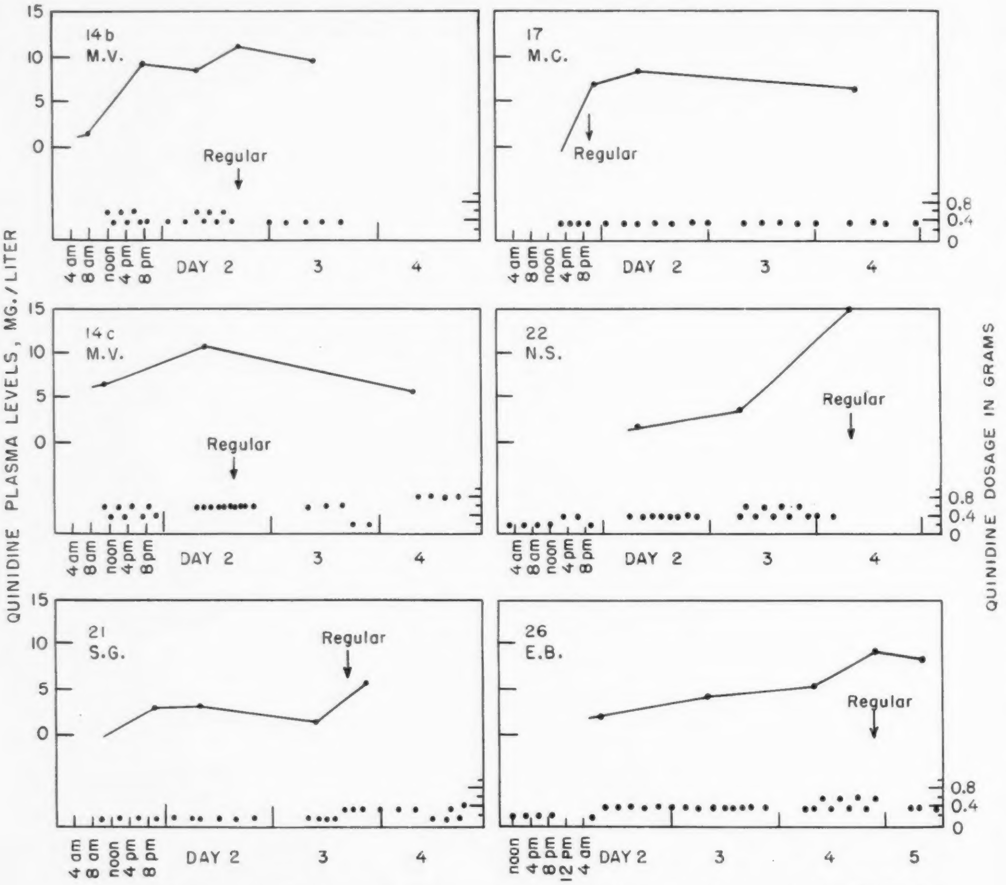

FIG. 1.—Plasma quinidine concentration curves of six patients in whom auricular fibrillation was converted to a regular sinus rhythm.

Table 2 shows those patients in whom auricular fibrillation was converted to sinus rhythm, the quinidine plasma concentrations at the time of conversion, the type of heart disease encountered in each patient, the duration of the auricular fibrillation, and the time and dosage needed to bring about conversion. The duration of auricular fibrillation varied in this group from eighteen hours to seven years; there was no direct correlation between the quinidine plasma concentration at the time of conversion and the duration of the auricular fibrillation.

The one patient (Case 14, *b* and 14, *c*, fig. 1), in whom auricular fibrillation was converted to sinus rhythm on three occasions, had quinidine plasma concentrations which were approximately the same at each time of conversion; 10.8 the first time, four months later 11.7, and

one month thereafter 14.0 mg. per liter. This implies that in the same patient there is some consistency of the concentration necessary for conversion of auricular fibrillation to regular sinus rhythm on different occasions. Four months after the third conversion the patient again entered the hospital for quinidine therapy: at a plasma quinidine concentration of over 11.5 mg. per liter she became quite ill owing to vomiting, diarrhea, and giddiness, and the treatment was discontinued without (Case 15, fig. 2). The patient received a total of 43.0 Gm. of quinidine in the nine days before sinus rhythm was established. On the ninth day he was given a 1.0 Gm. of quinidine every one and one-half hours. He manifested most of the toxic symptoms previously mentioned except for a fall in blood pressure. The cumulative dosage curve is shown at the bottom of figure 2; the gradual increase in quinidine dosage is indicated by the increasing slopes of the individual curves, each representing the adminis-

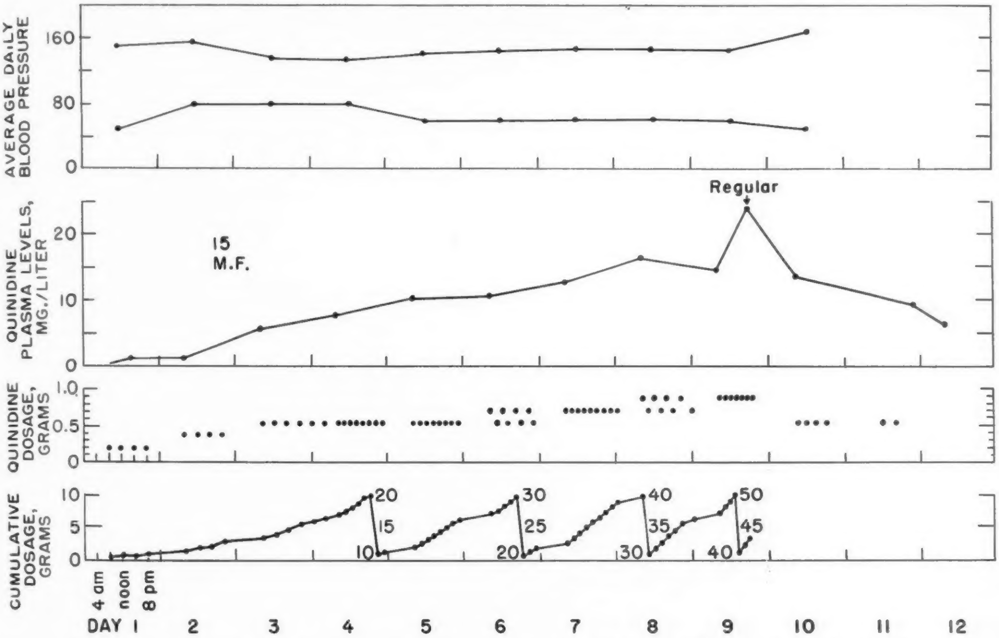

FIG. 2.—Plasma quinidine concentration curve in Case 15 (M.F.) with auricular fibrillation illustrating diminishing cumulative effect of successive dosage totaling 43.0 Gm. in nine days.

conversion of the auricular fibrillation. The plasma quinidine concentrations at which conversion took place in this patient gradually rose on each of the first three courses of treatment, suggesting that the patient was becoming more resistant to the action of the drug.

The highest quinidine plasma concentration obtained in any of these patients was 23.7 mg. per liter; this occurred at the time of conversion in a 38 year old man with a history of rheumatic aortic insufficiency for ten years and an initial attack of auricular fibrillation beginning one week prior to the onset of therapy tration of 10.0 Gm. of quinidine. The initial 10.0 Gm. were given in four days; 10.6 Gm. were administered in less than twenty-four hours prior to conversion. All blood specimens were obtained each morning before administration of the first daily dose of quinidine with the exception of the specimen drawn at the time of conversion which occurred approximately at 5 P.M. on the ninth day after 7.0 Gm. of quinidine were given in ten and one-half hours. There was a gradual but persistent increment in the plasma quinidine concentration curve even though the total dosage was

approximately the same on several days. Thus, on both the fourth and fifth days 4.8 Gm. of quinidine were given and on both the seventh and eighth days 7.2 Gm. were given. Although there was a rise in the plasma quinidine concentration from days four to five and from days five to six, the increment on the fourth day was greater than on the fifth. Also the increment on days seven to eight was greater than on days eight to nine, though equal dosage of quinidine was given in both instances. Linenthal, Ulick, and Patterson[7] observed a phenomenon similar to this when they administered smaller doses. They gave equal doses repeatedly and noted that the increment of plasma quinidine concentration ceased after four to five doses. It should be pointed out that since the plasma quinidine concentrations were taken each morning the concentrations during the day undoubtedly were much higher than indicated on the curve. It is to be noted at the top of the graph that the blood pressure changed very little during the entire nine days. This case likewise illustrates the need to overlook the many minor toxic manifestations of quinidine and the need for persistence in the administration of the drug to accomplish the desired goal.

The patients with rheumatic heart disease had higher quinidine concentrations at the time of conversion than did those with arteriosclerotic coronary heart disease. Also, those with rheumatic heart disease required a longer time and a larger dose of quinidine to effect conversion. This may imply that mechanical factors of valvular disease or auricular muscle damage influence the resistance of auricular fibrillation to conversion to sinus rhythm by quinidine therapy.

Summary and Conclusions

1. The toxic symptoms and signs and the plasma quinidine concentrations at which they were observed were discussed. It was not possible to predict what evidence of toxicity would appear at various plasma quinidine concentrations by comparing individual cases. The extreme variation in the dosages given and in the plasma contents at the time gastrointestinal irritability occurred suggests that such symptoms are due to local effects on the gastrointestinal tract. Likewise it was not possible to determine which of the toxic symptoms and signs were related to idiosyncrasy or hypersensitivity. Significant fall in blood pressure was thought to fit into this category. A fall in blood pressure was the only toxic symptom or sign other than extreme malaise and ventricular ectopic rhythm which was considered as an adequate reason for discontinuing quinidine therapy.*

2. In one patient in whom similar doses of quinidine were repeated on successive days the twenty-four-hour increment of plasma quinidine concentration was significantly less on the second day. With increased doses, however, greater increments could be produced.

3. The plasma quinidine contents observed in a series of 11 patients (thirteen instances) in whom auricular fibrillation was converted to sinus rhythm were discussed. Higher plasma quinidine concentrations were noted at the time of conversion in those with rheumatic heart disease than in those with arteriosclerotic coronary heart disease.

Acknowledgments

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* Two cases of transient ventricular fibrillation following two doses of 0.2 Gm. quinidine sulfate orally have been observed since this paper has been sent to press. Such phenomena should be classed as idiosyncrasies. Although not encountered in this series, a marked delay in the intraventricular conduction period (QRS.) of the electrocardiogram has been reported as a sign of serious quinidine intoxication. The death of a patient during quinidine therapy, presumably with ventricular fibrillation, was observed at another hospital. Three hours prior to death, and after 6.0 Gm. of quinidine had been given in forty hours, the QRS. period was prolonged to 0.2 second.

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Blood Quinidine Concentrations as a Guide in the Treatment of Cardiac Arrhythmias

By Maurice Sokolow, M.D., and A. L. Edgar, M.D.

Blood quinidine determinations by the photofluorometric method were made in 30 patients with auricular fibrillation or flutter in whom conversion to sinus rhythm was attempted. Successful conversion occurred in 82 per cent of the patients, with a mean blood level of 5.9 mg./liter. Vomiting and, in one case, ventricular tachycardia were the most important toxic manifestations. Doses of 0.4 to 0.6 Gm. every two hours for five doses daily were usually adequate to obtain the average conversion blood level. The importance of the quantitative aspects of quinidine therapy and the relation of time, dose and concentration of quinidine in the blood are discussed.

THE desirability of quantitative studies of blood concentration in relation to dose and therapeutic effect of a drug has been emphasized in recent years. Experiences with penicillin, the sulfonamides, and the salicylates have demonstrated that more rational therapeutics result from such studies. There exists a diversity of opinion in the literature regarding the indications and methods of the administration of quinidine.[1–13] The fact that quinidine has variously been used in an empiric manner accounts in part for this lack of uniform experience and opinion. The recent study by McMillan and Welfare[12] has demonstrated the excellent results that can be obtained with quinidine in the treatment of auricular fibrillation, and has emphasized the need for a re-evaluation of quinidine therapy.

The development during the war of more satisfactory analytic methods for study of various basic organic compounds, including quinidine, afforded opportunity for more detailed investigation than in the past. Several papers have appeared recently[14–17] which utilize quantitative measurements, but the data are incomplete. The present study was undertaken to determine the effective blood quinidine levels required for conversion of cardiac arrhythmias in individual patients, to determine whether or not such levels are comparable in different individuals, to determine the most satisfactory dose schedule to achieve such levels, and to learn something further about the absorption and excretion of quinidine.

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Method

A number of technics for measuring the concentration of quinidine in biologic samples have been described. Referring to basic organic compounds in general, Brodie states that "the simplicity and speed of fluorometric assay recommend it as the method of choice when possible."[18] Quinidine and allied cinchona derivatives exhibit a natural fluorescence in acid media and are therefore well suited to this method of analysis. Two fluorometric procedures have been described by Brodie and his co-workers.[19, 20] One involves the direct measurement of fluorescence in protein-free plasma filtrates, the other the extraction of the biologic samples with suitable solvents to remove degradation products before the final determination of fluorescence is made. Referring to the first of these methods, Brodie states that "... it has the advantage of speed and simplicity, but it lacks specificity, since interfering metabolic derivatives of the compound (quinine or quinidine) are not removed."[19] From Brodie's work, and from our own in a separate study, it is clear that this simpler method gives consistently higher levels than does the more specific extraction procedure.[20, 26]

In the present study the extraction method of analysis was used, the actual procedure followed being based on Linenthal's adaptation[15, 21] of the Brodie method. Briefly, it is carried out as follows:

A sample of urine or serum is added to distilled commercial ethylene dichloride, the mixture alkalinized with 10 per cent sodium hydroxide, and shaken for ten minutes in a mechanical agitator.

The aqueous phase is separated by centrifugation and removed by aspiration. With serum, no further extraction is required, but two additional washings with sodium hydroxide are necessary to assure removal of quinidine degradation products from urine. An aliquot of the urine or serum extract is diluted with ethylene dichloride and acidified with trichloracetic acid. Absolute ethanol is added to minimize adsorption. The fluorescence is then measured in the Coleman photofluorometer. The extraction in an identical manner of a blank specimen of serum or urine containing no quinidine permits determination of the net fluorescence of quinidine contained in the unknown sample. This is then compared with the net fluorescence of two standards containing known amounts of quinidine. With slight modifications in the technic, tissue and fecal samples may also be analyzed for their quinidine content.

Further details of our experience with the technical aspects of the method will be the subject of a separate communication.[26] The method has proved accurate in known dilutions within 8 per cent; the accuracy was considerably less with blood concentrations below 2 mg. per liter, unless twice the usual serum sample was used. The specificity of the method has been investigated by Linenthal and his associates,[15, 12] and no interference found from such commonly used drugs as aspirin, codeine, morphine, Demerol, phenobarbital, Seconal, pentobarbital, thiamine hydrochloride, ascorbic acid, menadione, sulfonamides, penicillin, digitalis, insulin and stilbestrol.

Subjects and Methods

The present study includes 72 patients in whom measurements of quinidine concentration in blood or urine were made. The data on conversion of auricular flutter and fibrillation are based on results in 3 patients with auricular flutter and 27 with auricular fibrillation* in whom it was thought that conversion to sinus rhythm was indicated according to the criteria outlined by the National Research Council.[22] The remaining 42 patients were receiving quinidine for a variety of reasons (prevention of paroxysmal arrhythmias, after myocardial infarction, or after chest surgery). In 4 of the 27 patients with auricular fibrillation, the arrhythmia was of less than one week duration and was considered acute. Table 1 summarizes the causes of the auricular arrhythmia in the cases studied. The patients were first fully digitalized in order to produce a slow ventricular rate, and maintenance doses of digitalis were then continued. If cardiac failure was present, rigid restriction of sodium and use of mercurial diuretics were employed as required to improve the cardiac failure as much as possible before attempted conversion. All patients were hospitalized and frequent clinical observations, electrocardiograms, and simple hemodynamic studies, such as vital capacity, circulation time, venous pressure, and exercise tolerance were studied before and after conversion in most instances. Patients were kept at bed rest while quinidine was being given. After preliminary studies, and in the light of previous clinical experience, two different schedules were used, more commonly the first: (1) quinidine was given every two hours for five to six doses, and (2) quinidine was given every four hours day and night. Frequent blood levels of quinidine were determined throughout the day and in most cases blood levels were obtained at the time of conversion. If relapse occurred, levels were determined at the time of relapse. If conversion to sinus rhythm was not accomplished, the peak blood level obtained by the dose schedule employed was noted. In many cases, total urine quinidine excretions were obtained and the relationship of dose given and quinidine excreted studied.

* This includes 2 cases of auricular fibrillation who were given quinidine in small doses to control ventricular premature beats. Both converted to sinus rhythm unexpectedly (Cases J. L. and A. O.).

Results

Of the 72 patients in whom pharmacologic data was obtained, attempts at conversion to sinus rhythm were made thirty-four times in 30 patients with auricular fibrillation and flutter. Sinus rhythm was re-established twenty-eight times in 24 patients, while six attempts in 6 patients failed. This represents a conversion rate of 82 per cent. Table 2 summarizes the details of total dose of quinidine, peak blood levels, and evidences of toxicity.

Figure 1 illustrates the blood levels obtained in the cases converted to sinus rhythm as well as in those who did not. The mean peak blood level in the cases in whom sinus rhythm was restored was 5.9 mg. per liter. In 75 per cent (twenty-one of twenty-eight attempts) the peak levels were between 4 and 9 mg. per liter. In only two of the twenty-eight attempts were levels above 10 mg. per liter successful in restoring sinus rhythm. Levels above 9 mg. per liter were reached in 6 patients, but resulted in only two conversions to sinus rhythm. Of the six failures, levels of 7 mg. per liter or above were obtained in all, and four did not convert despite levels of 10 mg. per liter or above. In contrast, in 71 per cent of the successful conversions (twenty in twenty-eight attempts), the peak level was below 7 mg. per liter.

In 5 cases, conversion occurred with peak levels of less than 4 mg. per liter. In one of

these (H. M.), auricular fibrillation had been present for a year following thyroidectomy for Graves' disease. Conversion occurred after five doses of 0.4 Gm. of quinidine every four hours rhythm occurred with only two doses of 0.2 Gm. of quinidine two hours apart at a level of 2 mg. per liter. In another similar case (L. C.) auricular fibrillation had been present for only

TABLE 1.—*Data on the Conversion of Arrhythmias with Quinidine: Summary of Thirty Cases (Thirty-four Attempts)*

	Converted	Failed	Relapsed	Time of Relapse	Reconverted	Remarks
I. Auricular Fibrillation (27 Cases) *Acute* (4)						
1 after pneumonectomy (E.F.)	1	0	1	1 day	1	
2 after auricular flutter (M.G., L.C.)	2	0	0		0	
1 associated with H.T.C.V.D. (R.B.)	1	0	0		0	
Chronic (23)						
11 with R.H.D.*	7	4†	2	2 wk. (C.G.) 12 hr. (V.H.)	1 (C.G.)	(C.G.) Reconversion not included in data since done elsewhere and no blood levels available (V.H.) No attempt to reconvert
3 with coronary disease (M.G., J.L., L.S.)	3	0	2	1 wk. (M.G.) 3 da. (L.S.)	No attempt	(J.L.) Converted unexpectedly while treating P.M.B.‡ Follow-up now 5 mos.
4 with thyrotoxicosis (T.B., H.M., F.B., A.O.)	3	1 (F.B.)	1	10 mo. (T.B.)	1	(T.B.) Relapsed again 1 wk. after 2nd conversion, not reconverted. (H.M.), followed 1 yr. (A.O.), Converted during treatment P.M.B.‡
1 with calcified pericardium (V.O.)	0	1	0		0	Early case; probably would use larger dose now.
4 with undetermined cause (C.N., W.Y., M.D., A.T.)	4	0	3	1 wk. (C.N.) 6 mo. (A.T.) 10 da. (W.Y.)	2 (W.Y., A.T.)	(C.N.) No attempt to reconvert
II. Auricular Flutter (3 Cases)						
1 with R.H.D. (L.G.)	1	0	0		0	
2 undetermined cause (F.D., F.W.)	2	0	1	6 mo. (F.W.)	1 c̄ dig, 1 c̄ quin.	(F.W.) Regular 2 mos. after relapse
Totals	24	6	10			
Summary	28 conversions in 34 attempts (82 per cent)					

* Patients: B.A., T.G., C.G., L.H., J.M., M.C., D.C., M.L., L.W., D.R., V.H.
† Patients: J.M., T.G., M.L., D.R.
‡ Premature beats.

at a blood level of approximately 3.1 mg. per liter. In the second (F. G.), a patient in whom auricular flutter had been converted to auricular fibrillation with digitoxin five days before quinidine was begun, conversion to sinus twenty-four hours following conversion of auricular flutter with digitalis and responded to 0.6 Gm. quinidine in four hours at an approximate serum level of 2.3 mg. per liter. The fourth case (A. O.) was under treatment for Graves'

Table 2.—*Summary of the Data on Twenty-four Patients Converted to Sinus Rhythm with Quinidine (Twenty-eight Conversions)*

Case	Age	Sex	Etiology and Duration of Arrhythmia	Dose of Quinidine (Gm.)	Peak Level (mg./liter)	Toxicity and Comment
B.A.	44	F	Rheumatic heart disease—3 months	2.6 in 2 days	7.5	None
T.B.	49	F	Post-thyrotoxicosis — 14 months	3.0 in 2 days	5.8	None
			Same 10 months later, 1 month after relapse			
M.C.	45	F	Rheumatic heart disease—12 months	2.6 in 2 days	8.0	None
C.F.	66	M	Chest surgery 2 days before. Still fibrillating 6 days after onset.	1.2 in 1½ days	7.0	None
			Quinidine then started. Relapse 24 hours after conversion at level of 3.8	2.0 in 1½ days	5.5	No toxicity
F.G.	64	F	Coronary heart disease—5 days	0.4 in 4 hours	2.0	Nausea 1–2 hours after conversion
M.G.	63	M	Coronary heart disease—3 months	6.2 in 2½ days	7.0	Nausea, headache, mental confusion, second day
C.G.	39	M	Rheumatic heart disease—2 months	8.2 in 3 days	15.8	Anorexia first day; nausea second day; decreased hearing and weight loss third day
L.H.	42	F	Rheumatic heart disease—3 weeks	4.2 in 2 days	4.8	None
H.M.	56	M	Post-thyrotoxicosis—18 months	2.4 in 1½ days	3.1	None
C.N.	55	F	Unknown etiology—4 months	2.4 in 1 day	5.7	None
L.S.	64	F	Coronary heart disease—2 months	1.8 in 1 day	4.0	None
A.T.	29	M	Unknown etiology—1 month	5.4 in 4 days	6.7	Tinnitus
			Relapse 6 months later—3 weeks	3.0 in 1 day	5.4	Slight tinnitus
D.C.	45	F	Rheumatic heart disease—1½ years	2.0 in 1 day	4.6	Vomiting, headache, tinnitus
W.Y.	62	M	Unknown etiology and duration. Quinidine discontinued 5 days after conversion.	4.0 in 1½ days	6.2*	None
			Relapse 4 days later. Treatment started same day.	1.8 in 16 hours	4.2*	None
M.D.	67	M	Unknown cause—3 months	4 in 3 days	5.8	None
J.L.	69	M	H.T.C.V.D., V.P.M.B.'s	1.6 in 24 hours	3.3*	None
A.O.	44	F	Thyrotoxicosis, V.P.M.B.—3 years	1.7 in 24 hours	1.3*	None
L.W.	42	F	Rheumatic heart disease—6 weeks	9.3 in 3½ days	7.0*	None
L.C.	45	M	Treatment of auricular flutter with Cedilanid, 24 hours	0.6 in 4 hours	2.3*	None
V.H.	43	M	Rheumatic heart disease—prob. 3 years	8.4 in 3 days	8.3	Slight nausea on second day with level of 7.9
R.B.	53	F	H.T.C.V.D.—6 days	2.0 in 24 hours	5.7*	Anorexia, nausea, weakness after second dose, level of 3.3
L.G.	41	F	Rheumatic heart disease—6 days	2.4 in 1 day	6.2	Nausea, vomiting, tinnitus, headache, 2 to 3 hours before conversion
F.W.	66	M	Coronary heart disease—3 weeks	5.8 in 4½ days	10.0*	None
F.D.	58	M	Coronary heart disease—24 hours	4.4 in 3 days	5.4	None

* Approximate level.

disease (sedation, propyl thiouracil) and was given quinidine to suppress ventricular premature beats. Conversion of auricular fibrillation unexpectedly occurred after 1.7 Gm. had been given (0.1 Gm. test dose, followed by 0.4 Gm. four times a day) at an approximate level of 1.3 mg. per liter. In the fifth case (J. L.) auricular fibrillation had been present for an unknown number of months. He had had cardiac failure for the previous seven weeks. The patient responded to 1.6 Gm. of quinidine in twenty-four hours at an approximate level of

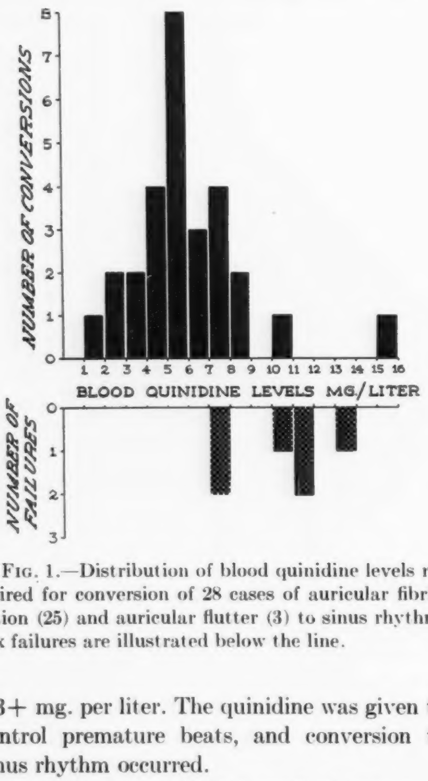

FIG. 1.—Distribution of blood quinidine levels required for conversion of 28 cases of auricular fibrillation (25) and auricular flutter (3) to sinus rhythm. Six failures are illustrated below the line.

3.3+ mg. per liter. The quinidine was given to control premature beats, and conversion to sinus rhythm occurred.

The amount of quinidine required to convert the patients to sinus rhythm was usually 0.4 or 0.6 Gm. every two hours for five doses. In only one instance was the dose of 0.8 Gm. every two hours for five doses employed (fig. 2, C.G.). The commonly advocated dose of 0.2 Gm. every two hours for five doses infrequently produced a blood level of as much as 4 mg. per liter and therefore was usually ineffective.

Clinical Pharmacology

In addition to therapeutic considerations, some data are available on the clinical pharmacology of quinidine. The rise in blood quinidine level with successive doses of the drug bore an inverse relationship to the rate of auricular contractions in both auricular fibrillation and auricular flutter (fig. 3, *a*, *b*). This was particularly true in the first twelve hours and supports the concept that the blood quinidine levels reflect the cardiac effects of the drug.

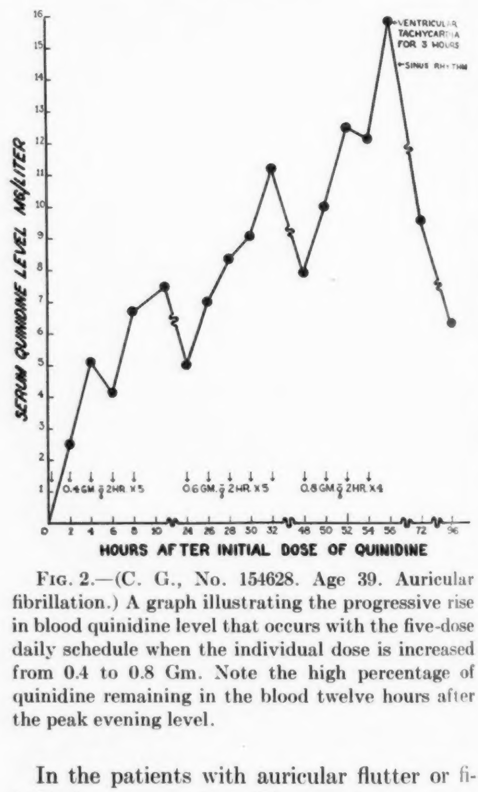

FIG. 2.—(C. G., No. 154628. Age 39. Auricular fibrillation.) A graph illustrating the progressive rise in blood quinidine level that occurs with the five-dose daily schedule when the individual dose is increased from 0.4 to 0.8 Gm. Note the high percentage of quinidine remaining in the blood twelve hours after the peak evening level.

In the patients with auricular flutter or fibrillation, conversion did not always occur when the blood level was at its peak. In 2 cases (T.B. fig. 4, and L.G.,) it followed by approximately two hours, and in 5 others (T.B., C.G., C.N., M.G., M.D.) occurred during the night after the peak level had passed.

After a given dose of quinidine, the maximum blood level was usually reached in approximately two hours; the level at the end of one hour at times was found to be approximately

30 per cent that of the two hour level as shown in the following 3 patients:

Case	Dose (Gm.)	Blood Level (mg./liter) One hour	Two hours
V.T.	0.4	0.8	2.3
J.G.	0.2	0.45	1.1
J.G.	0.4	0.45	1.3

The blood level invariably was lower four hours after a given dose than at the peak two-hour level, the decrement usually being in the neighborhood of 10 to 20 per cent, as indicated in the following cases in which levels two and four hours after a given dose are listed. All patients in this group had been given multiple doses of quinidine.

Case	Blood Level (mg./liter) Two hours after dose	Four hours after dose
A.T.	6.7	5.6
A.T.	5.4 (1½ hrs.)	4.0
C.N.	5.7	4.6
H.M.	2.9	2.7
H.M.	3.9	3.1
M.G.	7.0	6.4
M.G.	4.4	3.7
L.G.	6.2	5.8
E.F.	7.0	5.6
M.C.	8.0	7.3
T.B.	5.5 (3 hrs.)	4.0
L.H.	2.8	2.0
V.	7.0	6.5

In view of textbook statements that quinidine is rapidly excreted and that the effect of a given dose by mouth ceases in four to five hours,[10] it was of interest to find that significant levels remained in the blood for some twelve to twenty-four hours (fig. 5). The average residual blood level twelve to eighteen hours after the last dose was 42 per cent of the previous peak level (20 patients, thirty-six levels). The average residual blood levels the next morning after three commonly used conversions schedules are tabulated below:

0.2 Gm. every two hours for five doses = 1.8 mg./liter (8)*

0.4 Gm. every two hours for five doses = 2.5 mg./liter (14)*

0.6 Gm. every two hours for five doses = 3.9 mg./liter (7)*

Total number of cases in each group.

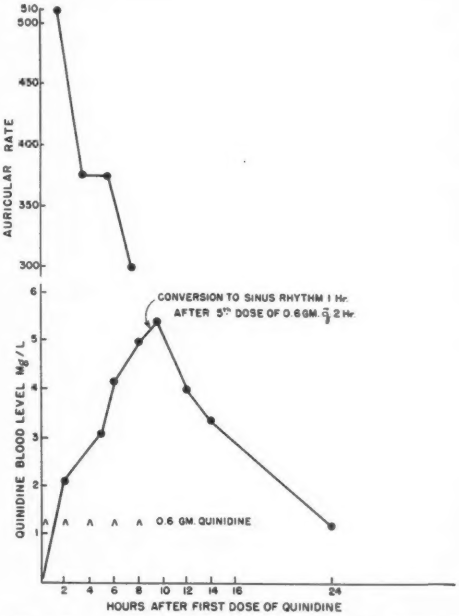

FIG. 3a.—The relationship between the decrease in the auricular rate and rise in blood quinidine concentration in a case of auricular fibrillation (A. T., U 120498. Male, age 29).

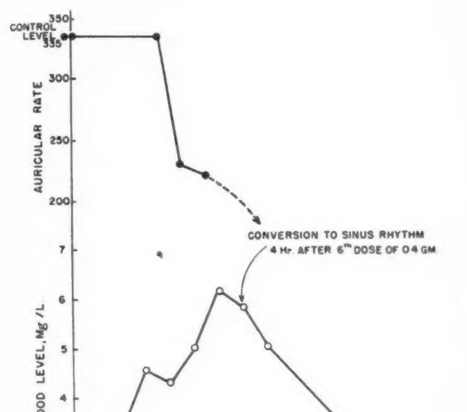

FIG. 3b.—The relationship between the decrease in the auricular rate and rise in blood quinidine concentration in a case of auricular flutter (L. G., U 1577699. Female, age 41).

Measurable residual levels were found for as long as seventy-two hours after the last dose of quinidine in one patient, for fifty-six hours in another, and for thirty-three hours in a third. No attempt was made to determine the length hours, the increment obtained with each of the first two doses was found to be 1.5 mg. per liter, almost double the increment (0.8 mg. per liter) obtained with subsequent doses. When the same dose was repeated every two hours, the level

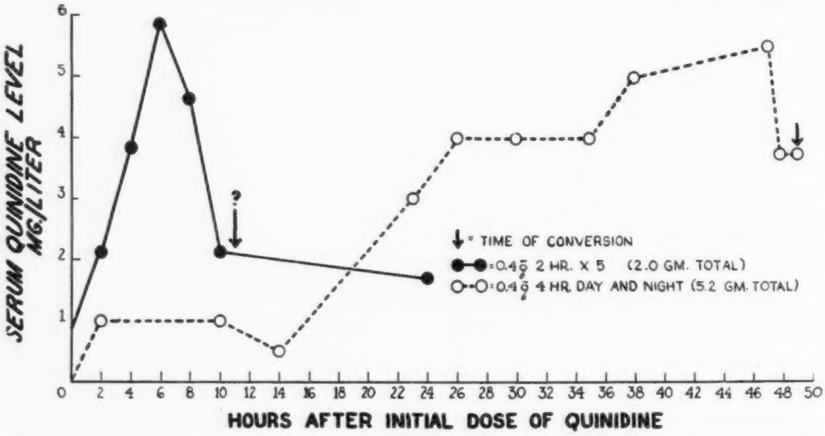

FIG. 4.—Comparison of two- and four-hour dose schedules in a patient with two episodes of auricular fibrillation ten months apart (T. B., No. 134316, age 49).

of time quinidine remained in the blood in the other patients.

When quinidine was given every two hours for about five doses (four to six) the net increment in blood level rose as the size of the individual dose was increased. The average net increase in blood level (peak level minus residual level that morning) with several dose schedules was:

0.2 Gm. every two hours for 5 doses = 3.9 mg./liter (8)*
0.4 Gm. every two hours for 5 doses = 4.9 mg./liter (16)*
0.6 Gm. every two hours for 5 doses = 5.7 mg./liter (7)*

When 0.2 Gm. was given, the average net increase (level two hours after last dose minus that morning's residual level) was 3.9 mg. per liter (average of 8 patients). With 0.4 Gm. it was 4.9 mg. per liter (average of 16 patients), and with 0.6 Gm., 5.7 mg. per liter (average of 7 patients). When quinidine was given in this manner, the increment produced by successive doses became less after the first few doses. In 13 patients who were given 0.4 Gm. every two

* Total number of cases in each group.

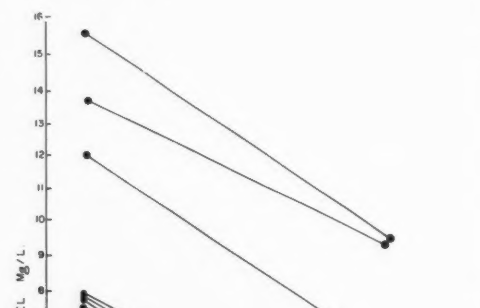

FIG. 5.—The amount of quinidine remaining in the blood ten to twenty hours after the last evening dose is illustrated in the graph showing the relative decrement in blood concentration.

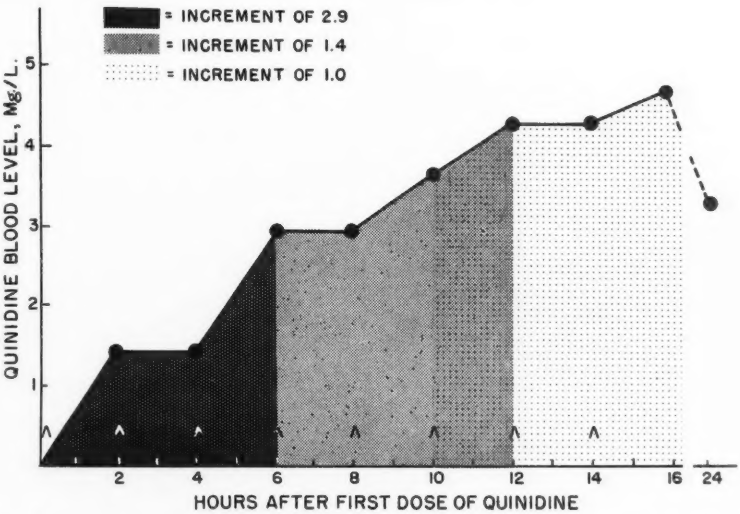

FIG. 6.—Decreasing increment of blood quinidine level with successive doses of 0.4 Gm. each (M. G., U154360. Male, age 63).

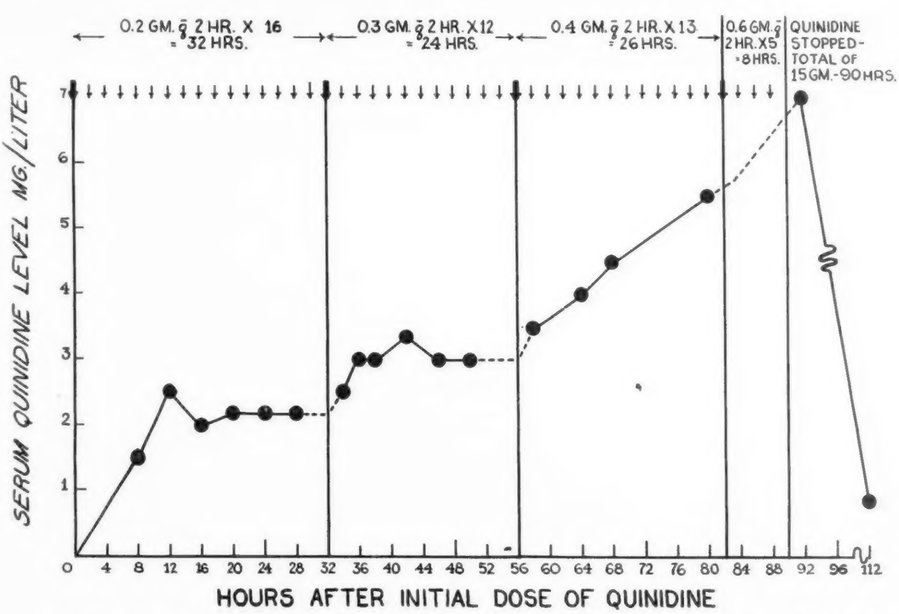

FIG. 7.—The failure of repeated doses of quinidine 0.2 and 0.3 Gm. each to produce further increases in blood concentration after the first four or five doses (F. B., No. 161359, age 57. Auricular fibrillation).

increased more after each of the first two doses than it did after later doses. This tendency is illustrated in figures 6 and 7. This same decreasing effect following multiple doses of the same size may be shown in another way by comparing the increase in level resulting from the first two doses together with that resulting from all the remaining doses together (usually

two to four more, but in some cases, five or six more). With 0.4 Gm. given every two hours, the first two doses resulted in an average increase of 3.1 mg. per liter in 13 patients, while the subsequent three or four doses resulted in an increase of only 2.3 mg. per liter. It is therefore apparent that the initial two doses produced greater effect than did subsequent doses, even if four or five more were given.

This "adaptation" mechanism was similarly observed when patients were given quinidine every four hours day and night or were given the same dose of quinidine at any fixed interval (fig. 8). It was observed when the four-hour interval was used that the peak blood level reached a maximum on the second and third day, maintained a plateau for several days, and then often fell so that at the end of a week the blood level was approximately equal to that which was obtained at the end of the first day. Further experience with fixed daily doses of quinidine has shown that in some cases the daily maximum blood level falls only slightly or not at all after the peak levels have reached a plateau in two to five days. This may represent equilibration between the tissues and the blood. In rare instances, the peak blood level may not be reached for a week after fixed daily doses. It is apparent that if higher blood levels were desired, increasing the size of the individual dose or the frequency of administration would have been necessary to raise the blood level. When a given dose of quinidine was given every two hours, the increment in blood level became progressively less after the first three or four doses and after the sixth dose, no further rise in blood quinidine level was obtained with 0.2 Gm. and 0.3 Gm. amounts despite six or

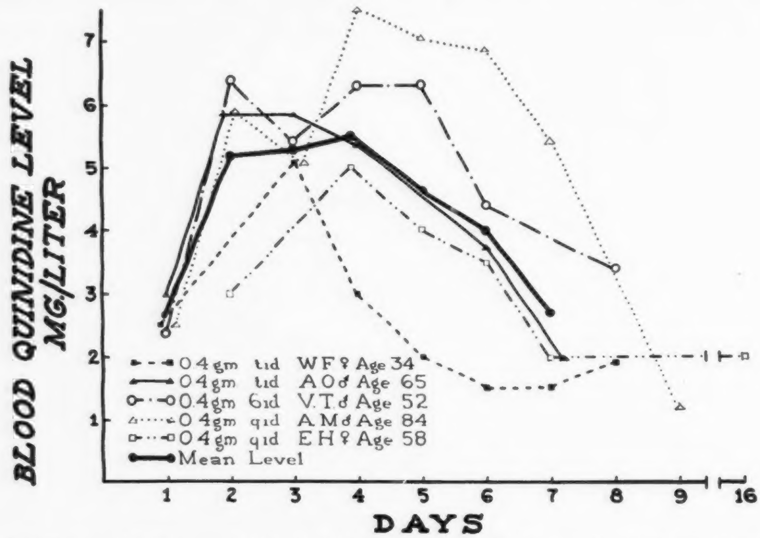

FIG. 8.—The parabolic curve obtained with fixed daily doses of quinidine, illustrating that an "adaptation" mechanism prevents maintenance of the highest blood levels.

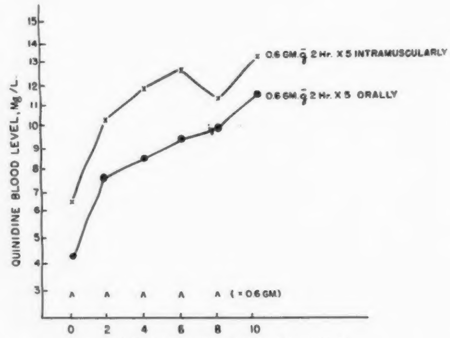

FIG. 9.—Comparison of blood levels obtained with 0.6 Gm. every two hours for five doses orally and intramuscularly in a case of chronic auricular fibrillation. Same patient on successive days. First line represents residual. (J. M., U 59617. Male, age 51.)

even subsequent doses unless the size of the individual dose was increased (fig. 7).

Two patients with chronic auricular fibrillation were given the same dose schedule of quinidine at separate times orally and intramuscularly (fig. 9), using the urea-antipyrine solution described by Sturnick and his associates.[23] In both patients the time of maximum blood level and the curves of ascending blood level were essentially similar with the two routes of administration. The levels rose at about the same rate, reached the same peak and declined in a similar manner.

Relapses

Ten patients who had been converted to sinus rhythm relapsed to their original arrhythmia at intervals of fourteen hours to seven months (including C.G.). The data is summarized below for each case.

Summary of Six Patients With Auricular Fibrillation in Whom Quinidine Failed to Restore Sinus Rhythm

Case 1. F. B., male, age 57 years: Thyrotoxicosis. Auricular fibrillation of ten years' duration (postthyroidectomy). Heart moderately enlarged, 35 per cent, especially the left ventricle. A level of 7 mg. per liter was reached without converting the arrhythmia. Quinidine was discontinued although the only evidence of toxicity was mild nausea.

Case 2. T. G., female, age 57 years: Rheumatic heart disease with mitral stenosis. Auricular fibrillation of at least five and one-half years' duration. Heart enlarged moderately. Functional Class III despite maximum improvement with digitalis and a low caloric, low salt diet. Quinidine dosage was somewhat irregular but a level of 11 mg. per liter was reached with a dose of 0.6 Gm. every two hours for six doses, at which time the patient noted tinnitus and slight deafness. The rhythm remained irregular and further trial of higher doses was not attempted.

Case 3. M. L., female, age 52 years: Rheumatic heart disease with mitral stenosis. Auricular fibrillation for at least two and one-half years, probably for four years. Heart size +35 per cent, moderately enlarged, especially the left auricle and right ventricle. The patient had been on digitalis for four years, since the appearance of symptoms of cardiac failure. She failed to convert at a level of 7.0 mg. per liter after 0.4 Gm. every two hours for five doses on two successive days, followed by 0.6 Gm. every two hours for five doses the third and fourth days. Quinidine was stopped because of repeated vomiting.

Case 4. J. M., male, age 51 years: Rheumatic heart disease with mitral stenosis. Auricular fibrillation, probably of at least three years' duration. Slight left auricular and left ventricular enlargement. Onset of failure three years ago, and borderline failure continued despite the use of digitalis and sodium restriction. Two major embolic episodes occurred, the first to the left femoral arteries one year ago necessitating amputation, and the second to the right femoral artery with subsequent claudication, two years ago. The patient failed to convert despite a level of 13.7 mg. per liter after having received 0.4 Gm. every two hours for 5 doses the first day, and 0.6 Gm. every two hours for five doses on each of the two following days (the last course being given intramuscularly). Quinidine was discontinued because of persistent severe nausea and repeated vomiting.

Case 5. V. O., female, age 49 years: Calcific pericarditis of unknown etiology. Auricular fibrillation probably of eighteen months' duration and generalized cardiac enlargement. History of "enlarged" heart twenty years ago with symptoms of weakness and dyspnea. Occasional palpitations for five years with a marked increase in this complaint eighteen months ago. The patient was digitalized three months ago when she was told that she had a "case" around her heart. Symptoms of increasing failure appeared two months ago which responded to mercurials, bed rest, and sodium restriction. She received several courses of quinidine and reached a maximum level of 10 mg. per liter on the fourth day with 0.4 Gm. every four hours day and night. Quinidine was discontinued although no evidence of toxicity was present at the time. (There had been vomiting ten days before, while the patient was receiving 0.4 gm. every two hours for 5 doses.)

Case 6. D. R., female, age 34 years: Rheumatic heart disease with mitral stenosis. Auricular fibrillation of three months' duration. Heart slightly enlarged. The patient received 5.0 Gm. in twenty-four hours (0.6 to 0.8 Gm. every four hours) which resulted in a peak level of 11.3 mg. per liter, but failed to restore sinus rhythm. She then received 0.6 Gm. approximately every four hours, for thirteen doses, but failed to convert despite blood levels of 6.5 to 0.6 mg. per liter during the three-day period. There was no evidence of important toxicity.

Four of the patients were reconverted easily and no attempt was made in the other patients.* Of the ten relapses, seven occurred within two weeks after conversion. Four of the

* One of these 6 patients (C. G.) relapsed and was reconverted with small additional doses of quinidine by an outside physician. He then maintained regular rhythm. He is considered a relapse but not included in our reconversion data because no blood levels are available.

patients who relapsed had received no maintenance quinidine and the maximum maintenance dose in the other 5 patients was 0.2 Gm. four times a day. In the light of subsequent experience in the prevention of paroxysmal arrhythmias, and in the suppression of premature beats,* this amount of quinidine was probably insufficient. It was of interest to note that in the patients reconverted after a lapse of six months, the blood levels required for conversion were essentially the same (A.T., fig. 10, and T. B., fig. 4). When Patient A.T. was first converted, the dose had been gradually raised from an initial regime of 0.2 Gm. every two

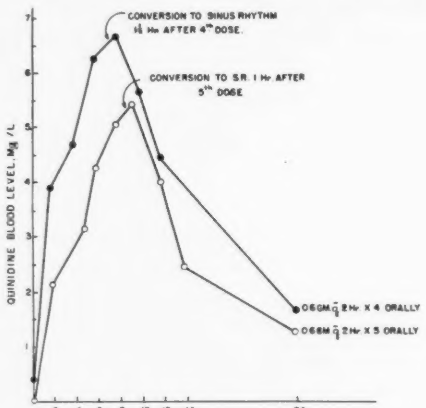

FIG. 10.—Comparison of conversion levels on separate occasions six months apart in a case of auricular fibrillation, with 0.6 Gm. every two hours given both times. (A. T., U 120498. Male, age 29.)

hours for five doses to a final successful schedule of 0.6 Gm. every two hours for five doses on the third day, with a peak blood level of 6.7 mg. per 100 cubic centimeters cent. When the patient relapsed, he was given 0.6 Gm. in five two-hourly doses with successful conversion on the same day, at a peak blood level of 5.4 mg. per cubic centimeters.

One patient (T.B., fig. 4) with chronic auricular fibrillation was treated initially with 0.2 Gm. every two hours for five doses, followed the next day by 0.4 Gm. every two hours for five doses. Sinus rhythm was established during the night after the last 0.4 Gm. dose had been given (total of 2.0 Gm.). Ten months later, the patient again developed auricular fibrillation and this time was given 0.4 Gm. every four hours day and night. Conversion took place after a total of 5.2 Gm. had been given. Figure 4 shows the levels in this patient. It can be seen that peak levels were similar, but the total dose required and the time necessary to achieve the peak levels were much greater when the quinidine was given every four hours.

* Report in preparation.

Urinary Excretion

Studies of urinary excretion of quinidine were carried out in 26 patients. During the first day of quinidine therapy, an average of 4.8 per cent of the first twelve hour dose was excreted in the urine during the same period (average of 14 cases). An average of 10.1 per cent (11, 11, 11.5, 8.5, 8.4, 10.5 and 9.6 per cent) of the first twelve hour dose appeared in the urine during the first twenty-four hours (7 cases). In 12 patients who were receiving fixed maintenance doses of quinidine, the average amount found in the twenty-four hour urine was 15.5 per cent (range of 9 to 24 per cent) of the daily dose, (average of eighteen studies). In 12 of the 18 patients, the amount of the daily dose excreted in twenty-four hours varied between 12 per cent and 16 per cent. In one patient (T.B.) who was taking 0.4 Gm. quinidine every four hours, day and night, the 6 per cent of the first twenty-four hour dose was excreted in the same period; in the second twenty-four hours, the amount rose to 11 per cent, and in the third twenty-four hours, to 20 per cent. In 6 patients in whom serial urine collections were made following discontinuance of quinidine, measurable amounts remained in the urine for fifteen hours in 1, twenty-four hours in 2, thirty hours in 1, and thirty-six hours in 2. (In one of the latter, it was present for thirty-six hours on two different occasions.)

Toxicity

Table 3 summarizes the toxic symptoms noted in our patients converted with quinidine. In 2 patients, vomiting precluded further use of the drug, and one patient underwent a short bout of ventricular tachycardia shortly after conversion. This complication occurred at the

high blood level of 15.8 mg. per liter in a patient who had severe mitral stenosis, marked cardiac enlargement and previous cardiac failure. Conversion had been attempted and quinidine given in large doses because two major arterial emboli had occurred in the previous two months. In the remainder of the cases the toxic symptoms of nausea, diarrhea, tinnitus and headache were of relatively minor degree. Frequent electrocardiograms were taken during conversion and in no case were conduction defects obtained. In a number of patients, auricular flutter occurred as the rapid auricular rate of auricular fibrillation was slowed with quinidine. In only one patient in whom auricular flutter was produced did the ventricular rate rise with a 2:1 block when this occurred just prior to conversion. When quinidine was stopped, the auricular rate rose and auricular fibrillation was again present the next day. In the remaining patients the ventricular rate was essentially unchanged despite the development of auricular flutter. Maintenance doses of digitalis were continued in these patients.

The Prevention of Paroxysmal Arrhythmias

Delevett and Poindexter[14] described 2 cases in which critical blood levels could be defined for the prevention of paroxysmal tachycardia. A study of this phase of therapy is in preparation, but one striking case may serve to illustrate the value of blood levels in the prevention of paroxysmal ventricular tachycardia (fig. 11).

TABLE 3.—*Summary of Toxic Manifestations of Quinidine in the Thirty Patients with Auricular Flutter or Fibrillation in whom Conversion was Attempted*

Case	Symptoms	Degree	Blood Level at Time (mg./liter)	Conversion Level (mg./liter)	Comment
L.G.	Tinnitus, headache, vomiting	+	4.3	5.8	None
M.G.	Nausea, headache, v.p.m.b.'s	+	5.0–7.0	4.4	None
T.B.	Diarrhea, tinnitus, headache	++	4.2	4.0	None
A.T.	(1) Tinnitus	+	5.4	6.7	None
	(2) Tinnitus	+	2.2	5.4	
C.N.	Faintness	++	5.0	4.6–2.1	Pulse 140 with 2:1 flutter just prior to conversion
V.O.	Nausea, vomiting	++	6.3	Failed at 10	None
F.G.	Nausea	+	2.0	2.0	None
T.G.	Tinnitus, slight deafness	+	11.0	Failed at 11	None
J.M.	Diarrhea, vomiting	+++	6.3	Failed at 13	None
F.B.	Nausea	+	7.0	Failed at 7	None
C.G.	Anorexia	+	7.5		None
	Nausea	++	10.0	15.8–9.6	
	Decreased hearing	+	12.5		
	Ventricular tachycardia	3 hrs.	15.8		
M.L.	Vomiting and diarrhea	+	5.0	Failed at 6.9	Vomiting with same blood level obtained by intramuscular quinidine
	Vomiting	++++	6.9		
D.C.	Vomiting	+	2.75		None
	Headache	+		4.6	
	Tinnitus	+	4.6		
V.H.	Slight nausea	+	5.0	8.3	None

The patient was a 63-year-old man with coronary artery disease, in whom ventricular tachycardia of four days' duration was converted to sinus rhythm with 3.4 Gm. quinidine in sixteen hours. The conversion level was 4.1 mg. per liter. During the subsequent two and one-half weeks, while the patient was receiving maintenance doses, he had five recurrences of arrhythmia, and it was possible to establish the approximate effective therapeutic blood

quinidine level necessary to maintain sinus rhythm. Levels taken during four of the paroxysms of tachycardia were 3.3, 3.5, 3.3, and 4.2 mg. per liter. Levels at the time of reconversion of three of the attacks were 4.3, 5.6, and 4.6 mg. per liter. Maintenance doses thereafter were adjusted to keep the level above 4 mg. per liter and no arrhythmia occurred during the remainder of his one-month hospital stay. The patient has since been followed for nine months, and maintained on 3 Gm. (2.8 to 3.2) quinidine daily which produces mid-day blood levels constantly between 5 and 5.5 mg. per liter. Since resuming his normal activities, he has had occasional transient episodes of tachycardia but none have been persistent and only three have required additional quinidine, the longest responding in seven hours to 0.8 Gm. in addition to the maintenance dose. After being free of attacks for several months, while receiving 3 Gm. quinidine daily and maintaining a blood level of 5 mg. per liter, the patient was placed on quinidine "enseals" in the same dosage. His blood level fell to 1.7 mg. per liter and he had a prolonged (twenty-four hour) attack of ventricular tachycardia that responded to oral ordinary quinidine. He was again given ordinary quinidine and has had no further attacks, the blood level again rising to 5 mg. per liter.

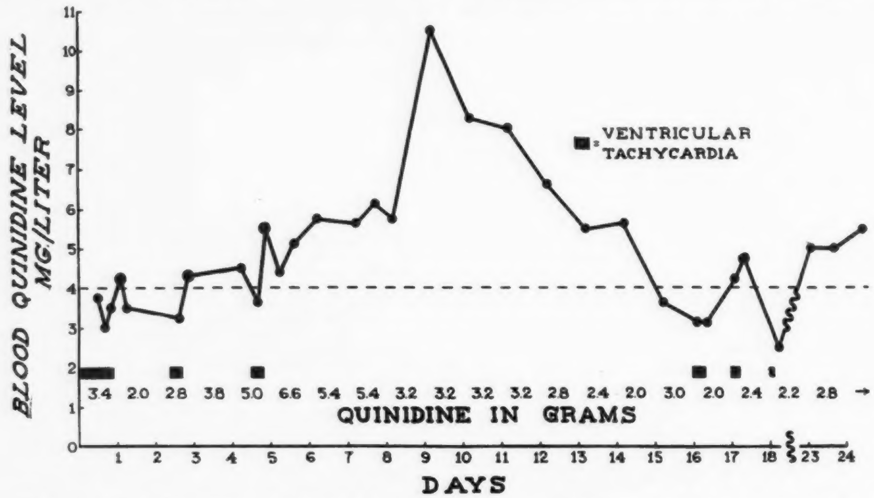

Fig. 11.—The importance of determining the critical blood level required to prevent attacks of paroxysmal ventricular tachycardia. Small additional doses of quinidine increased the blood concentration above the critical level and restored normal rhythm whenever the blood concentration fell below 4 mg. per liter. (W. R., male, age 63. Coronary heart disease. Recurrent ventricular tachycardia for three years.)

Data on Relapses: Auricular Flutter and Fibrillation

Of the 24 patients (twenty-eight instances) converted to sinus rhythm, 10 have relapsed. Five of those who relapsed were reconverted with quinidine. No further quinidine treatment was attempted in the other 5 patients. One was reconverted elsewhere and is not included in our data.

Case 1. E. F., male, age 66 years: Postpneumonectomy, auricular fibrillation. Conversion was accomplished with 6 doses of 0.2 Gm. every four hours at a level of 7.0 mg. per liter. The patient relapsed twenty-four hours later, after receiving three or more doses of 0.2 Gm. (twice on the day of conversion, once the following morning) at a level of 3.8 mg. per liter. He was then reconverted with 0.4 Gm. every four hours for four doses, at a level of 5.5 mg. per liter.

Case 2. M. G., male, age 63 years: Coronary heart disease with chronic auricular fibrillation. Conversion was accomplished with 0.4 Gm. every two hours for eight doses, followed the next day by 0.6 Gm. every two hours for four doses, and the third day by 0.6 Gm. for one dose. The blood level at this time was 4.4 mg. per liter. The patient received 0.4 Gm. four times a day for two days and was discharged home on 0.2 Gm. four times a day. When seen one week later, his rhythm was irregular, but reconversion was not attempted.

Case 3. L. S., female, age 64 years: Coronary heart disease with chronic auricular fibrillation. Conversion was accomplished with 0.4 Gm. every four hours for four doses at a level of 4.0 mg. per liter.

The patient then received 0.3 Gm. every six hours for the next three days and relapsed the morning of the fourth day. No attempt was made to reconvert the rhythm.

Case 4. A. T., male, age 29 years: Auricular fibrillation. This patient gave a history of recurrent prolonged attacks of auricular fibrillation of unknown etiology for ten years. The patient had been having two to three attacks a year which were controlled by quinidine in each instance. He was converted to normal rhythm at a time when the blood level was 6.7 mg. per liter. Relapse occurred approximately six months after conversion, but no maintenance doses of quinidine had been taken during that period. He was reconverted with 0.6 Gm. every two hours for 5 doses and the blood level was 5.4 mg. per liter.

Case 5. F. W., male, age 66 years: Auricular flutter. This patient had recurrent auricular flutter of unknown etiology. He had had two previous entries into the University of California Hospital for purposes of conversion. On the third entry, he was converted with 2.8 Gm., given in doses of 0.4 Gm. every four hours, after having had 0.2 Gm. and 0.4 Gm. every two hours for five doses on the two previous days; the blood level at time of conversion was 10 mg. per liter. Six months later, the patient relapsed, having received no maintenance doses of quinidine during this period. The patient was reconverted with digitoxin and three months later, his rhythm was still regular on various doses of quinidine.

Case 6. C. N., female, age 55 years: Auricular fibrillation. This patient had chronic auricular fibrillation of unknown etiology. She was converted with a blood level of 5.7 mg. per liter after 0.4 Gm. every two hours for six doses. She was discharged home on 0.2 Gm. four times a day which she stopped five days later. A few days later, auricular fibrillation reappeared. No further attempt was made to reconvert the arrhythmia.

Case 7. W. S. Y., male, age 62 years: Auricular fibrillation. The duration of the auricular fibrillation is not definite, although it had probably been present for months. The etiology was not definite. The arrhythmia was converted to sinus rhythm with 0.4 Gm. every four hours for five doses, followed the next day by 0.6 Gm. every four hours for four doses, at a blood level of 6.2 mg. per liter. The patient was then given 0.4 gm. four times a day for two days, and 0.2 Gm. four times a day for two days. No quinidine was taken for four days, after which the patient relapsed. The administration of 0.6 Gm. for three doses brought about reconversion. The patient is currently on a schedule of 0.4 Gm. three times a day without relapse.

Case 8. T. B., female, age 49 years: Auricular fibrillation. Auricular fibrillation occurred in the patient following a thyroidectomy, and had been of fourteen months' duration. Conversion resulted at a blood level of 5.8 mg. per liter after 0.4 Gm. every two hours for five doses, and the patient was discharged home on 0.2 Gm. four times a day for five days. One week later, auricular fibrillation was again present, but was converted when the quinidine dosage was increased to 0.4 Gm., 0.4 Gm., 0.2 Gm., and 0.2 Gm. A second relapse occurred two weeks later (the quinidine dose had been reduced by 0.2 Gm.), and conversion was brought about by increasing the daily dose by 0.2 Gm. Thereafter the patient's rhythm remained regular, and the quinidine dosage was gradually reduced. After two and one-half months, the quinidine was stopped, and regular rhythm was maintained without quinidine for four months, after which time another relapse occurred. Conversion at this time was accomplished with 0.4 Gm. every four hours for thirteen doses with a blood level of 5.5 mg. per liter. The patient was discharged home on 0.4 Gm. three times a day, on which dose she relapsed, and did not reconvert with 0.4 Gm. five times a day for three days. No further attempt to reconvert was made.

Case 9. C. G., male, age 39 years: Rheumatic heart disease with mitral stenosis and auricular fibrillation. The auricular fibrillation had been present for two months. The patient had a femoral embolus in June, 1948, which was presumably the result of paroxysmal auricular fibrillation. Sinus rhythm was present during the patient's stay in the hospital. He had a cerebral embolus in the fall of 1948 and at this time, and for the next two months, auricular fibrillation was present. Conversion was accomplished at a peak level of 15.8 mg. per liter. Two weeks later, there was a relapse on a maintenance dose of 0.2 Gm. three times a day. The arrhythmia lasted four days, in spite of increasing the dose to 0.2 Gm. four times a day. A second relapse lasting ten days occurred one week later, while the patient was on a maintenance dose of 0.2 Gm. four times a day. Regular rhythm was restored by increasing the dose to 0.4 Gm. four times a day with a blood level of 7.9 mg. per liter. Since then, the patient's rhythm has remained regular on 0.4 Gm. three times a day and a level of 5.6 mg. per liter.

Case 10. V. H., male, age 43 years: Rheumatic heart disease and auricular fibrillation. Auricular fibrillation had probably been present in this patient for three years. It was converted to normal rhythm after 8.4 Gm. in three days with a peak blood level of 8.3 mg. per liter. The fourth morning, arrhythmia was again present, fourteen hours after conversion, despite doses of 0.6 Gm. two times during the night. No blood level was obtained. No further attempt at reconversion was made.

Discussion

The data presented indicate that the use of quinidine blood levels may provide a more rational basis for the use of quinidine in the treatment of auricular fibrillation and auricular

flutter. The fact that peak levels occur in two hours and that the increase in level becomes progressively less after four to five doses indicates that the total amount of quinidine is not as important as the number of hours over which the quinidine is given and the size of the individual dose. Any given dose schedule, therefore, may fail if these factors are not taken into account.

The value of the blood level of quinidine as a guide in therapeutic conversion of auricular fibrillation and flutter is significant. Most patients were converted to normal rhythm at moderate blood levels. In resistant cases, even when higher blood levels (greater than 9 mg. per liter) were attained, only a small percentage converted (in only 2 of 6 cases). Only 2 patients in whom sinus rhythm was produced required levels exceeding 10 mg. per liter, and in one of them a short bout of ventricular tachycardia resulted. It is of interest that in the 6 patients in whom sinus rhythm was not restored, 4 failed with levels equal to or exceeding 10 mg. per liter. It would appear, therefore, that if successful conversion does not occur with moderate doses and moderate blood levels, forcing the issue with higher doses is only infrequently successful and adds considerably to the possibility of important toxicity. Four of the 6 patients who failed to convert to sinus rhythm had mitral stenosis with hearts that varied in size from but slightly to markedly enlarged.

It was of considerable interest that several patients converted to sinus rhythm at low blood levels with doses of quinidine given not for conversion but for the suppression of premature beats. Since approximately 15 per cent of our patients had normal rhythm restored at blood levels of 4 mg. per liter or less, and since this blood level rarely is attended by any toxicity, one may well wonder if small doses of quinidine might be tried in many cases in which a serious attempt at conversion is not warranted. One may be pleasantly surprised to gain successful results with small doses of quinidine.

The occasional delay in conversion after the peak blood level has passed suggests the possibility of a time element in the action of quinidine on the heart. In this respect, the observations of Weiss and Hatcher[24] are of interest; these workers found that the cat heart may be paralyzed by very high blood stream concentrations of quinidine before much absorption by the myocardium has occurred, whereas with prolonged lower blood concentrations, much higher myocardial levels may be reached without paralysis.

The adaptation of the body to continued administration of quinidine is even more clearly shown in the parabolic curve obtained when the same dose of quinidine is given day and night. The fact that the blood level may rise for the first seventy-two hours with this type of dose schedule only to fall gradually as this same dose schedule is continued makes it clear why some patients may convert on the second or third day of a fixed schedule. However, it also emphasizes the futility of continuing this routine if success is not obtained after the first few days. To increase the blood level of quinidine, the drug must then, after a few days, be given at more frequent intervals or in larger individual doses.

The minor toxicity and high percentage of successful conversions supports the opinion that the dangers of the use of quinidine have been overemphasized. Many of our patients had less dyspnea, less palpitations, were able to do more work, and, in general, were distinctly improved following successful conversion to sinus rhythm. This improvement resulted despite the fact that the ventricular rate when the rhythm was sinus in origin was essentially the same as that obtained in the well-digitalized auricular fibrillation, and despite the fact that often no significant change in vital capacity, circulation time, or venous pressure could be demonstrated.

The successful conversion to sinus rhythm of 2 patients who recently had had serious arterial emboli while fibrillating (C.G. and V.H.) emphasizes the possible benefit to be obtained in sinus rhythm in these patients.[7] The most common cause of arterial embolism in the series of Allen, Barker and Hines[25] occurred in patients with auricular fibrillation. No instances of em-

bolism occurred following conversion in the present series of cases.*

The relatively small percentage of quinidine that is excreted in the urine in relation to the dose given (even when given intramuscularly) indicates that the disappearance of quinidine from the blood is through metabolic processes, the exact nature of which are not known. Similarly, the adaptation phenomena by which the body responds to fixed daily doses of the drug remains unexplained.

Our observations that many patients with auricular fibrillation progress through a stage of auricular flutter under the influence of quinidine as the auricular rate is slowed support the notion that both arrhythmias may be similar in mechanism and differ mainly in the rate of discharge of the ectopic focus.[27] The frequency with which auricular flutter is noted probably depends in part on the frequency with which electrocardiograms are taken as the conversion time approaches. The danger is present of a sudden rise in ventricular rate, as may occur if a 2:1 block develops,[1] but this happens infrequently.

Summary and Conclusions

1. Blood and urine quinidine levels using the photofluorometric method of Brodie, as modified by Linenthal, were obtained in 72 patients, including 30 with auricular fibrillation and auricular flutter in whom conversion was attempted.

2. Successful conversion to sinus rhythm occurred in twenty-eight of thirty-four attempts in 30 patients (82 per cent). The average peak blood level in the cases converted was 5.9 mg. per liter; 75 per cent of the patients converted to normal rhythm at levels between 4 and 9 mg. per liter. These blood levels were obtained with quinidine dose schedules of 0.4 or 0.6 Gm. every two hours for five doses.

* One patient who converted to sinus rhythm after the present series was completed developed symptoms and signs compatible with a pulmonary embolus coincident with relapse of auricular fibrillation. He did well and no definite diagnosis was made. Another patient, being prepared for conversion, developed a cerebral embolus and died before quinidine therapy was started.

3. Blood levels higher than 9 mg. per liter were obtained in 6 patients but resulted in conversion to sinus rhythm in only 2 patients. Of the twenty-eight successful conversions, only 2 patients required levels of 10 mg. per liter or more. Of the 6 patients in whom normal rhythm was not restored, levels of 10 mg. per liter or more were obtained in 4 patients. The likelihood of successful conversion is relatively small if large doses and high blood levels are required.

4. Important toxic manifestations occurred in 3 patients; in 2, vomiting of sufficient degree precluded further treatment, and in one patient a short bout of ventricular tachycardia occurred. In the last patient, a high blood level of 15.8 mg. per liter was required for successful conversion.

5. Data on the clinical pharmacology of the drug have been described and information on the time of peak blood levels, duration of effect, and decrement of blood levels has been noted.

6. The time-dose relationship with fixed dose schedules and the adaptation phenomena have been discussed. The importance of the size of the individual dose and the necessity of being aware of the parabolic blood quinidine curve resulting from fixed daily dose schedules has been emphasized.

7. The inverse relationship in the first twelve hours of the auricular rate as obtained by right precordial electrocardiograms and blood quinidine levels indicates that the blood levels reflect cardiac effects of the drug.

Acknowledgments

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Congenital Heart Disease with Septal Defects in which Paradoxical Brain Abscess Causes Death

A Review of the Literature and Report of Two Cases

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The presence of septal defects in congenital heart disease makes for a direct shunting of particulate matter from the venous to the arterial side of the circulation. In reviewing the literature we have been surprised to find that this phenomenon, with resultant brain abscess, has been second only to bacterial endocarditis as a septic cause of death. The subject deserves attention from the viewpoint of early diagnosis and cure, since the reported mortality has been almost 100 per cent.

Although brain abscess resulting from septic paradoxical embolization is well established the correct clinical diagnosis is rarely made. We here present an analysis of the 42 cases reported to date and add 2 of our own.

Historical

At this writing there are thirty articles in the literature concerned with 42 reported cases. In 1814 Farre[14] discussed a case of tetralogy of Fallot in a boy aged 9 years who died of brain abscess. Lallemand,[23] Louis,[24] and Berthody[7] described similar cases, and in 1880 Ballet[4] reviewed the literature and added one case of his own.

By the end of the last century the entity of brain abscess due to septic paradoxical embolization was well known. In 1881, Peacock[27] reported such a case, and in recording the 45 cases of tetralogy described to that time stated: "The death of the patients is in the largest proportion of cases, as in the present instance, caused by cerebral disease. Two of my previously reported cases died in attacks of convulsions." Abbott and her collaborators[2] reported 2 cases in 1923 and reviewed the literature. Sutherland[15] stated in 1929: "It is an old standing clinical observation that cases of congenital heart disease often suffered or died with signs of cerebral abscess or embolism." In 1932, Rabinowitz and associates[29] were the first to report a case with a correct antemortem diagnosis. Wechsler and Kaplan[37] described 2 cases in 1940 which were diagnosed correctly; both patients succumbed in spite of surgical drainage of the abscesses. Excellent discussions of the subject are given by Robbins,[30] Hanna,[19] and Gates and co-workers.[16]

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Predisposing Factors

The presence of a septal defect with the chance shunting of organisms and infected material directly into the arterial system without the benefit of pulmonary filtering is the factor responsible for the brain abscess. It is interesting that in none of the patients were other secondary abscess sites found. There is a considerable polemic as to whether organisms alone by lodging in the brain tissue can produce an abscess without the benefit of previous trauma, local ischemia, or associated embolization with infected particulate matter. Two of Hanna's subjects[19] showed unquestioned pathologic evidence of cerebral infarction preceding the formation of abscess. Collis[9] gives a good discussion of the local factors involved.

Antecedent infection was found clinically or suspected and later verified post mortem in 15 of the reported cases. In 29 instances, including the cases herein reported, no primary source of infection was located (table 1). In none of the patients reported were any of the local head and face and intrathoracic sources of brain abscess found.

Bacterial endocarditis is not a factor. In 2 patients there was bacterial endocarditis of a stenotic pulmonic valve,[19, 35] but in these subjects the inclusion of the defect as part of the tetralogy of Fallot predicated the avoidance of pulmonary filtering by way of the septal defect.

Nature of the Abscesses

In forty-two instances it was possible to analyze the abscesses found. Thirty-seven

TABLE 1.—*Reported Cases of Brain Abscess Associated With Congenital Heart Disease*

Author	Year	Age (years)	Sex	Antecedent Infection	Cardiac Lesion	Location and Number of Abscesses	Microorganisms in Abscess
Farre[14]	1814	9	M	Unknown	Tetralogy of Fallot	Rt. cerebral hemisphere (1)	Unknown
Lallemand[23]	?	57	F	Unknown	Patent F.O., tricuspid and pulmonic stenosis	Rt. frontal lobe (1)	Unknown
Louis[24]	1838	25	M	Unknown	Basal ventricular septal defect	Rt. ant. corpus striatum (1); rt. optic tract (1)	Unknown
Berthody[7]	1845	21	F	Unknown	Basal I.V. septal defect; hypoplasia pulmonary artery	Left occipital lobe (1)	Unknown
Ballet[4]	1880	15	M	Unknown	Basal I.V. septal defect; aplastic rt. ventricle; tricuspid atresia; both atria open in left ventricle	Rt. frontal lobe (1)	Unknown
Peacock[a, 27]	1881	7	M	Unknown	Tetralogy of Fallot	Rt. ant. cerebrum (1)	Unknown
Stone[35]	1881	19	F	Unknown	Basal I.V. septal defect as part of tetralogy of Fallot[b]	Rt. occipital lobe (1)	Unknown
Northrup[25]	1894	4½	M	Unknown	Tetralogy of Fallot	Cerebral (1); location not given	Unknown
Acker[3]	1895	10	F	Unknown	Transposition of great vessels; basal I.V. septal defect; patent F.O. & ductus arteriosus	Not given	*Diplococcus lanceolatus*
Jacobi[22]	1895	29	M	Unknown	Basal I.V. septal defect	Lt. temporal lobe (1)	Unknown
Packard[26]	1895	?	M	Unknown	Basal I.V. septal defect; patent F.O.	Location unknown (1)	Unknown
Deneke[11]	1906	18	M	None	Tetralogy of Fallot; patent ductus arteriosus	Rt. cerebrum (1)	Streptococcus
Heigel[20]	1913	10	F	None	Ebstein's disease with patent F.O.	Left cerebrum (1)	Gram-pos. cocci & bacilli; gram-neg. bacilli
Abbott et al.[2]	1923	10	M	Phlegmon rt. arm	Tetralogy of Fallot	Brain not examined	Unknown
Abbott et al.[2]	1923	11	M	Acute appendicitis	Tetralogy of Fallot; patent ductus arteriosus	Lt. frontal lobe (1)	Streptococcus

TABLE 1.—*Continued*

Author	Year	Age (years)	Sex	Antecedent Infection	Cardiac Lesion	Location and Number of Abscesses	Microorganisms in Abscess
Raab[28]	1923	15	M	Unknown	Tetralogy of Fallot; patent F.O.	Rt. cerebrum (1)	Gram-neg. rods
Bach[5]	1928	30	M	Removal of 6 carious teeth	Tetralogy of Fallot; patent F.O.	Rt. postero-temporal (1)	Gram-pos. rods
Baumgartner & Abbott[6]	1929	21	M	None	Eisenmenger's complex	Rt. frontoparietal (1)	Hemolytic streptococcus
Rabinowitz et al.[c, 29]	1932	16	F	None	Tetralogy of Fallot	Cerebellar (1)	*B. coli*
Drey et al.[12]	1938	14	F	None	Cor biatriatum triloculare	Intraventricular cerebral (1)	Not done
Ingham[d, 21]	1938	39	F	Acute upper respiratory ininfection	Patent foramen ovale	Left temporoparietal (1)	Unknown
Wechsler & Kaplan[e, 37]	1940	14	M	None	Tetralogy of Fallot	Rt. frontoparietal (1)	Gram-neg. rods & diplococci.
Wechsler & Kaplan[f, 37]	1940	11½	F	Acute upper respiratory infection	Tetralogy of Fallot	Rt. frontal lobe (1)	*Streptococcus viridans*
Hanna[19]	1941	18	F	Unknown	Basal I.V. septal defect	Lt. internal capsule & thalamus (1)	Streptococcus
Hanna[19]	1941	34	F	Unknown	Basal I.V. septal defect	Lt. frontal lobe (1)	*H. influenzae*
Hanna[19]	1941	10	F	Unknown	Tetralogy of Fallot[g]	Lt. thalamus (1)	*H. influenzae*
Hanna[19]	1941	3	M	Unknown	Tetralogy of Fallot; bicuspid pulmonic valve	Rt. temporal lobe (1)	No organisms found
Hanna[19]	1941	19	M	Acute upper respiratory ininfection	Muscular I.V. septal defect; subpulmonic stenosis; pulmonary atresia	Rt. occipital lobe lobe (1)	Unknown
Hanna[19]	1941	46	F	Pain in knee, fever, 7 days	Atrial septal defect	Multiple infarcts & abscesses, rt. frontal lobe	Unknown
Ruhberg[31]	1942	6	F	Acute upper respiratory infection	Basal I.V. septal defect; pulmonary stenosis	Multiple abscesses, rt. occipital lobe	*B. coli*, *Staphylococcus albus*, hemolytic streptococcus
Vann & Miller[36]	1944	8	M	Pharyngeal abscess	Pseudomonoventricular heart; transposition great vessels; pulmonary stenosis	Rt. frontal lobe (1); lt. frontal lobe (1)	Unknown

TABLE 1.—*Continued*

Author	Year	Age (years)	Sex	Antecedent Infection	Cardiac Lesion	Location and Number of Abscesses	Microorganisms in Abscess
Robbins[30]	1945	10	F	Unknown	Tetralogy of Fallot	Lt. parieto-occipital (1)	Hemolytic streptococcus
Robbins[30]	1945	19	F	Severe pyorrhea, stomatitis	Tetralogy of Fallot; patent ductus arteriosus	Rt. parieto-occipital (1)	No growth (sulfonamide therapy)
Robbins[30]	1945	20	F	Unknown	Tetralogy of Fallot; patent ductus arteriosus	Left temporal lobe	No organisms on smear & culture
Sidenburg et al.[h, 32]	1946	6	M	Severe stomatitis & gingivitis	Tetralogy of Fallot	Lt. parietal lobe (1)	*B. pyocyaneus, Staph. aureus, B. coli*
Smolik et al.[i, 33]	1946	9	F	P.U.O. 2 wks. prior to onset abscess symptoms	Prob. I. V. septal defect with ? patent ductus arteriosus	Lt. frontal lobe (1)	*H. influenzae*
Gates et al.[16]	1947	6	M	Tonsillectomy	Cor biatriatum triloculare; patent F.O.	Lt. temporo-occipital (1)	Unknown
Gates et al.[j, 16]	1947	8	M	Unknown	Tetralogy of Fallot; patent F.O.	Rt. frontal lobe, posteroinferior (1)	Gram-neg. anaerobic rods
Gates et al.[k, 16]	1947	5	M	Unknown	Tetralogy of Fallot	Lt. frontoparietal (1)	Unknown
Gates et al.[16]	1947	26	F	Acute upper respiratory infection	Atrial septal defect	Rt. occipito-parietal (1)	*Actinomyces bovis*
Hand[m, 17]	1947	5½	F	Acute upper respiratory infection	Tetralogy of Fallot	Lt. temporal (1); lt. occipital (1); lt. parietal (1)	Gram-pos. diplococci
Hand[17]	1947	8	F	Unknown	Tetralogy of Fallot	Rt. temporal lobe (1)	Unknown
This report[n]	1949	9	M	None	Tetralogy of Fallot	Probably lt. parietal occipital	? Gram-pos. diplococci
This report	1949	35	F	None	Basal I.V. septal defect; patent ductus arteriosus	Lt. temporal lobe (1)	Hemolytic *Staphylococcus albus*

F.O. = foramen ovale; I.V. = interventricular; ant. = anterior

[a] Clinical diagnosis; necropsy limited to thorax.

[b] Acute endocarditis of lower pulmonary conus orifice.

[c] Correct clinical diagnosis.

[d] Correct clinical diagnosis; left temporoparietal decompression; death thirteen days postoperatively.

[e] Clinical diagnosis; abscess trephined; death in fifty days; no necropsy.

[f] Clinical diagnosis; abscess trephined; sulfapyridine therapy; death in forty-three days.

[g] Acute bacterial endocarditis on pulmonary valve (*H. influenzae*).

[h] Correct clinical diagnosis.

[i] Correct clinical diagnosis; surgical aspiration of abscess; complete recovery in two months.

[j] Correct clinical diagnosis; surgical drainage; death in twenty-nine days.

[k] Correct clinical diagnosis; death before localization of abscess.

[m] Correct clinical diagnosis; evacuation of abscess with apparent recovery; recurrence and death. Bacterial endocarditis of aortic valve.

[n] Clinical diagnoses; permission for necropsy denied.

were solitary whereas 5 patients had multiple abscesses. In 21 patients the abscesses were in the right hemisphere, in 15 they were left sided, and in one patient a cerebellar abscess was found. In 25 of the patients, a postmortem bacteriologic study of the abscess was attempted. Micro-organisms were identified on smear or cultured in 15 of these. The species were wide in range (table 1). Chronicity of the abscess occurred in the few patients who had benefit of chemotherapy or surgical intervention.

Diagnosis

In only 9 patients was the correct clinical diagnosis made. In 6, surgical drainage or decompression was performed, but only one patient survived.

Table 2.—*Age and Sex Distribution in Forty-three cases of Congenital Heart Disease with Paradoxical Brain Abscess*

Age (Years)	No. of Cases	
0–9	14	Age Range: 3 to 57
10–19	17	years
20–29	6	Average Age: 16.6
30–39	4	years
40–49	1	Sex Distribution:
50–59	1	Males 22
Age Unknown	1	
Total	44	Females 22

The diagnosis should be suspected in all patients with known congenital septal defects who have symptoms of central nervous system involvement. It should be especially suspected in young subjects. Although the age range of the patients included in this report varied from 3 to 57 years, the average age was 16.6 years (table 2). An overwhelming number of patients have a history of acute onset of fever, headache, and lethargy, often associated with nausea or vomiting. The lumbar puncture often reveals an increase in pressure and a slight to moderate increase in cells. It is this early predominant lymphocytosis, or even the complete initial absence of pleocytosis, so characteristic of early developing brain abscess, which often leads to a mistaken diagnosis of encephalitis or tuberculous meningitis. Blood and spinal fluid cultures should be made but diagnostic dependance upon them is to be decried. In the 44 cases reported, blood culture, when made, was consistently negative. Spinal fluid culture was attempted in 17 instances, and in the 5 patients in whom it was positive the abscess had ruptured with a resultant terminal meningitis.

Report of Cases

Case 1.—The patient, A. W., a 9 year old white boy, cyanotic since birth, was admitted to the Contagious Division, Cleveland City Hospital, on June 5, 1946. The admission diagnosis was "acute encephalitis." He had been treated since May 13 at another hospital with penicillin and sulfadiazine for an alleged "streptococcus infection" characterized by headache, fatigueability, and fever. Eighteen days prior to admission into this hospital the boy developed right facial weakness. No history of antecedent infection could be elicited.

The patient was acutely and chronically ill. The physical and roentgenologic findings were characteristic of the tetralogy of Fallot. Brudzinski's sign was questionably present bilaterally, there was weakness in the muscles supplied by the right facial nerve, and the speech was thick.

Laboratory Studies: The hemogram revealed a hemoglobin of more than 17 grams, and a red blood cell count of 9,000,000, with 10,000 white cells, predominantly polymorphonuclear leukocytes. On lumbar puncture the spinal fluid pressure was 390 mm. of water, the protein value was 55 mg. per 100 cc. of fluid, the chloride value 445 mg. per 100 cc. (as Cl), and the cell count 18 per cubic millimeter. Organisms could not be demonstrated in the blood and spinal fluid by culture or smear.

Hospital Course: The boy was given penicillin and sulfadiazine. The temperature throughout the hospital stay fluctuated between 36.8 and 39.8 C. On the second day, weakness of the right arm and leg developed. Sulfadiazine was discontinued because of gross hematuria, which did not recur. He seemed to be improving and the temperature became normal, but on the eighth day the temperature rose to 38.5 C., and the patient became confused. There was marked nuchal rigidity and sustained ankle clonus on the right. Lumbar puncture revealed 11,200 cells per cu. mm. of fluid, almost all of them being polymorphonuclear leukocytes. Gram-positive diplococci were seen on smear and grown on culture. On the nineteenth day the optic discs became fuzzy, right facial weakness was more pronounced, and there was tremor, dystereognosis, and paresis of the right arm and leg. The diagnosis of brain abscess in the left parieto-occipital area with rupture and secondary meningitis was suggested. The patient failed to respond to continued chemotherapy and died on the thirty-third hospital day.

Comment: Although necropsy was not permitted, it was obvious that this patient suffered from a veno-arterial shunt, which most likely was part of the tetralogy of Fallot. The course and findings were characteristic of a brain abscess producing a local, surface meningitis, followed by rupture into a lateral ventricle and flooding of the cerebrospinal fluid with pus. The correct diagnosis was made too late to be of benefit to the patient. A diagnosis was made initially of bacterial endocarditis with cerebral embolism, which was adhered to in spite of persistently negative blood culture (a common occurrence in brain abscess). Moreover, therewere no clinical findings to substantiate the diagnosis other than the presence of congenital heart disease of a type in which bacterial endocarditis is of low incidence.[1] In retrospect the circumstances were such that, coupled with the signs of early localization, a correct diagnosis could have been attained in two days following admission to this hospital.

Case 2.—The patient, J. D., a 35 year old Negro woman, known to have an interventricular septal defect, was first admitted to the Tuberculosis Division, Cleveland City Hospital, in 1937, because of far advanced pulmonary tuberculosis without cavitation. After two years' bed rest, she was followed in the Outpatient Department and continued to remain asymptomatic until March 22, 1947, when she complained of sudden onset of nausea, intermittent vomiting, severe headache, and fever, which continued unabated until March 30, when she became stuporous. She was seen by a physician, and admitted to the Contagious Division, Cleveland City Hospital, on April 1, 1947, with the diagnosis of acute encephalitis or tuberculous meningitis.

On admission the patient was semicomatose. The right optic disc showed slight papilledema. There was definite nuchal rigidity. The heart was not enlarged, and the murmur heard previously apparently had not changed. The lungs were clear to percussion and auscultation. The Kernig and Brudzinski signs were present, and the deep tendon reflexes were hyperactive on the left side.

Laboratory Studies: The red blood cell count was 6,400,000, the hemoglobin value 20 grams, and the white blood cell count 16,900; 90 per cent of the white cells were polymorphonuclear leukocytes. This picture may have been partially modified by the patient's extreme dehydration. The spinal fluid (lumbar puncture) was under 54 mm. of water pressure; there were 80 cells per cu. mm. of fluid, all of them being mononuclear leukocytes. Twenty-four hours later the spinal fluid contained 160 cells per cu. mm., 90 per cent of which were mononuclear cells; the protein value was 180 mg. and the chloride (as Cl) value 436 mg. per 100 cc. of fluid. Cultures of the spinal fluid and of the blood showed no growth.

Hospital Course: The patient remained unconscious, often moving aimlessly the left arm and leg, both of which showed marked increase in extensor tonus. She failed to regain consciousness and expired after forty-eight hours.

Necropsy: The heart weighed 350 grams. Both right and left ventricular walls measured 1 cm. in thickness. All valves were normal and no endocarditis was present. There was a basal interventricular septal defect which was oval and measured 1.5 cm. in the greatest diameter. The ductus arteriosus was patent, but the lumen was only 2 mm. in diameter. At the tip of the right temporal lobe was an acute globular abscess measuring 5 cm. in diameter, from which 60 cc. of foul-smelling pus were evacuated. Smears of this abscess showed many gram-positive cocci, and on culture a hemolytic *Staphylococcus albus* was grown. The mastoid air cells and accessory paranasal sinuses were normal. The leg veins were not thrombosed. In the lungs there was moderately extensive fibrosis and nodulation consistent with healed tuberculosis. No primary source of the acute infection was found.

Comment: This patient was practically moribund on admission, and there was little that could have been done diagnostically or therapeutically. As is common in patients with brain abscess, the blood culture, and spinal fluid smear and culture were all negative. Cognizance of the not infrequent complication of congenital heart disease with septal defects by brain abscess, coupled with the pointing history of sudden onset of symptoms and the suggestion of localization (extensor rigidity of the left sided extremities, right papilledema), might have led to immediate consideration of a diagnosis which was not even suspected.

Physiologic Considerations

For many years it has been speculated, partly on the basis of paradoxical embolization, that a right-to-left shunt must occur sometime during the cardiac cycle in the presence of septal defects. Physiologic studies on living patients by means of cardiac catheterization have now shown this to be true beyond dispute. In Fallot's tetrad the shunt is obvious, and Bing and associates[8] have shown that this shunting from right to left occurs in the absence of failure, owing to the overriding of

the aorta. This direct shunt is again obvious on anatomic grounds alone in the instances of complete transposition of the great vessels and of monoventricular hearts.

Until now it has been assumed that in the presence of a functionally patent foramen ovale or of an atrial septal defect the shunt is entirely from left to right until such time as failure supervenes, when a reversal of flow is said to occur, favoring paradoxical embolization. In instances in which failure was not demonstrable, chance interplay of blood currents at the orificial margin has been held responsible.[16] Cournand and colleagues[10] have studied this problem. By direct catheterization of right and left auricles in three young subjects with no evidence of failure, they demonstrated the overall preponderance of left-to right flow. They likewise showed that reciprocal admixture is distinctly possible. Simultaneous recording of pressures with a double-lumen catheter, however, is needed to prove this point definitely. Additional evidence is afforded by lower oxygen saturation of peripheral arterial blood during periods of exercise as compared to blood from the pulmonary vein.[18]

TABLE 3.—*Cardiac Lesions Encountered (Forty-four Cases)*

Tetralogy of Fallot	23
Basal interventricular septal defect	8
Patent foramen ovale and atrial septal defect	5
Cor biatriatum triloculare	2
Complete transposition of great vessels	1
Eisenmenger's complex	1
Muscular interventricular septal defect	1
Miscellaneous	1

In solitary ventricular septal defects it has not been demonstrated that a right-to-left shunt occurs in the presence of a totally unembarrassed right ventricle, but exercise tolerance tests have shown a decrease in peripheral arterial oxygen saturation in patients who at rest showed no evidence of failure.[18]

In the cases analyzed in this report, there were 9 instances of ventricular septal defect (table 3). Of these, one was not proved by necropsy. In 4 instances the defect was associated with pulmonary stenosis or hypoplasia, a factor which would enhance the load on the right ventricle and lead to increased opportunity for reciprocal blood admixture.

There were 5 instances of isolated defects in the atrial septum. In one, further embarrassment was caused by associated pulmonary stenosis, in the other by a displaced, insufficient tricuspid valve (Ebstein's disease).

There is no clear evidence in the 4 patients with solitary ventricular defects and in the 3 with atrial defects that early failure was not present. In all instances there was anatomic evidence of right-sided enlargement. None of these patients were younger than 18 years of age, which would point to a prolonged period of stress on the right side of the heart before failure becomes manifest.

Discussion

Robbins[30] has been quoted before, but it may not be amiss to cite him again: "In all probability, this apparent obscurity and paucity of reported cases represents the failure either of their recognition or of their publication, rather than the rarity of their occurrence." Maude Abbott[1] found 98 instances of bacterial endocarditis and endarteritis (17.6 per cent) in 555 autopsied congenital hearts. Gates and co-workers[16] reviewed 115 fatal cases of congenital heart disease. They found 5 instances of brain abscess (4.3 per cent) and 8 of bacterial endocarditis (7 per cent). Robbins[30] reviewed the records of 53 autopsy subjects who had congenital heart disease and found 3 instances of paradoxical abscess (5.6 per cent). Hanna[19] described 6 cases in a series of 160 autopsy subjects with congenital heart disease, an incidence of 3.8 per cent. This indicates that the condition is probably one-fourth as common as bacterial endocarditis, yet mention of this fact is rare; the diagnosis is usually missed, and many cases are probably not reported. The relative frequency of the condition is magnified when one studies the breakdown of Maude Abbott's cases. In 59 instances of transposition of the great vessels, bacterial endocarditis occurred in 6 patients (10 per cent); in 21 patients with cor biloculare and triloculare, none; in 31 patients with patent foramen ovale, none. The incidence was con-

siderably higher in patients with atrial septal and basal interventricular septal defects. This is in accordance with her explanation that "juxtaposition of the defect to the valvular endocardium and the attainment of a moderately advanced age are two factors that definitely increase the rate of frequency."

The great prevalence of solitary abscesses offers inducement to early diagnosis, as does the improved outlook for patients with the tetralogy because of the successful results of the Blalock-Taussig operation. In addition, Selzer and associates[31] have recently suggested remedial surgery in patients with pulmonary stenosis associated with patent foramen ovale. In one of our collected cases this combination of anomalies was presented.

Conclusions

1. Two cases of paradoxical brain abscess due to crossed septic emboli in patients with congenital septal defects of the heart are presented, and the literature is reviewed.

2. The incidence of this complication is probably much higher than is reported. As a specific bacterial cause of death in patients with congenital heart disease, paradoxical brain abscess stands second only to bacterial endocarditis.

3. Brain abscess should be suspected in all patients with congenital heart disease with septal defects presenting symptoms of central nervous system involvement.

4. Improvements in cardiac surgery, and the relative longevity of patients with isolated septal defects, particularly with the present availability of antibiotics, further justify all attempts to improve the poor therapeutic results reported to date.

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Arteriovenous Fistulas of the Lungs

By Samuel Baer, M.D., Albert Behrend, M.D., and Harold L. Goldburgh, M.D.,

Two cases of pulmonary arteriovenous fistula (or aneurysm) are presented, one of which is reported in detail. Twenty-three other cases of pulmonary arteriovenous aneurysm or fistula previously reported in the American literature are reviewed, and the clinical, laboratory, radiologic, physiologic, pathologic and hereditary features of this condition discussed. Clubbing of the fingers and toes, polycythemia and cyanosis are almost constant findings. The importance of differentiating this condition from polycythemia vera and congenital heart disease is emphasized.

PUBLISHED studies of pulmonary arteriovenous fistulas are not very common. There was no case of pulmonary arteriovenous aneurysm among the 111 cases of aneurysm of the pulmonary artery reviewed by Boyd and McGavack.[1] Brief case reports of malignant pulmonary hemangiomas were published in 1931[2] and 1935,[3] and in 1936 Bowers[4] reported a fatal pulmonary hemorrhage due to a benign hemangioma in a newborn infant. It was not until 1938, however, that Rodes's[5] detailed description of a case called attention to its occurrence in adults. Since then the accumulated reports[6–23] suggest that though pulmonary arteriovenous fistulas are relatively uncommon, the great majority have clinical and laboratory features which are typical and readily recognizable (table 1).

The disturbance is most apt to be found in the male, and all but five cases were recognized before the patient reached the age of 30 years. Cyanosis, clubbing of the digits, and polycythemia are the cardinal diagnostic findings. Dyspnea is an outstanding complaint and hemoptysis has occurred in one-third of the cases. Fainting, dizziness, convulsive seizures, and other cerebral manifestations are important secondary symptoms. At least half of the patients had telangiectasias or other vascular defects in the skin and mucous membranes. Abnormal pulmonary bruits were also present in 50 per cent of the cases.

As far as we are able to determine, the case we are reporting is the twenty-fourth on record in the American and English literature.* Others, however, have been observed but remain unreported. We believe this disturbance is important not because of its rarity and bizarre features, but because many such cases are probably masquerading under a diagnosis of congenital heart disease or polycythemia vera. In view of the ever-present risk of severe or even fatal pulmonary hemorrhage, and the possibility of cerebral complications, the advantages of early diagnosis and surgical correction become apparent.

Case Report

J. H., a white man, age 21 years, was first seen at the age of 14, in January 1941. During routine examination for an upper respiratory infection, marked cyanosis of the lips, and cyanosis and clubbing of the fingers and toes were noted.

He had been quite normal at birth. No specific abnormality in infancy was recalled by his parents. Since 1940 they had noted considerable duskiness of his lips and fingernails in cold weather and on vigorous exercise, especially swimming. Competition for the track team in high school had to be discontinued because of breathlessness. During a few months prior to the initial examination the patient had had a number of nosebleeds. The examination revealed a dusky cyanosis of the lips, fingernails, and toenails, with slight clubbing of the fingers and toes. The chest appeared completely normal. Neither by palpation nor percussion was the heart found to be enlarged; no thrills were felt. The heart sounds were of medium intensity and regular. A faint mitral systolic bruit was audible. Neither the liver nor spleen was palpable. The blood count revealed 107 per cent hemoglobin (Sahli) with 6,250,000 erythrocytes per cubic millimeter. The leucocyte and differential counts gave normal values. A diagnosis of polycythemia vera was made, and treatment consisting of weekly venesections was begun, 250 cc of blood being withdrawn during each treatment.

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* Since this paper was submitted for publication, an excellent discussion of this topic, listing 44 cases in the American and foreign literature, has been published by Yater and others (J.A.M.A., No. 141, page 581, October 1949).

Authors	Age	Sex	Cyanosis	Clubbing	Polycythemia	Dyspnea	Hemoptysis	Cardiac Enlargement	Bruit	Oxygen Saturation	Other Symptomas	Other Telangiectasias	Location by X-Ray Examination	Results
Rodes[5]	25	M	+	+	+	+	+	0	0		Fainting	Lips	Bilateral	Necropsy
Smith and Horton[6]	47	M	+	+	+	+	0	0	+				Right base	
Hepburn and Dauphinee[7]	23	F	+	+	+	+	0	0	0	73%	Fainting; slurred speech; dizziness		Right middle Right base	Pneumonectomy
Goldman[8]	22	M	+	+	+	+	0	0	0	70%	Dizziness; slurred speech; headache	Eye lid	Left lung	
Adams and co-workers[9]	24	M	+	+	+	0	+	0	0	71%	Epistaxis	Lip, face	Bilateral	Left pneumonectomy
Jones and Thompson[10]	24	F	+	+	+	0	0	0	+				Right lung	Pneumonectomy
Janes[11]	30	M	+		0	0	+	0	+			Lip	Bilateral	Local excisions
Alexander[12]	41	M	+	+	+	+	+	0	+		Dizziness		Bilateral	Necropsy
Sisson and co-workers[13]	45	F	+	+	0?	+	+	+	+		Dizziness; convulsions		Bilateral	Death following cardiac catheterization
Makler and Zion[14]	20	M	+	+	+	+	0	0	+		Headaches; epistaxis	Ear	Bilateral	
Whitaker[15]	48	F	+	+	+	+		0	0		Pain in chest	Face	Right lung	Lobectomy
Whitaker[15]	33	M		0				0	+		Pain in neck	Cheek, forehead	Left lung	
Cabot case[16]	23	F	+	+	+	+	0	0	0	89%	Bleeding gums		Right middle	Lobectomy
Beierwaltes and Byron[17]	27	F	+	+	+	0	0	0	0	77%		Face, palm	Right lower	Lobectomy
Burchell and Clogett[18]	20	M	+	+	+	0	0	0	+	74%	Tinnitus; headaches		Right base	Lobectomy
Bisgard[19]	29	M	+	+	+	+	0	0	+		Fatigue; fainting; cough; asthma	Lip	Right base	Lobectomy
Watson[20]	27	M	+	+	+	0	+	0	0				Right base	Lobectomy
Watson[20]	21	M	+	+	+	+	+		0		Headache; convulsion	Tongue, lips, eyelids, hands	Right base	Lobectomy
Maier and co-workers[21]	20	F	+	+	+	+	0	0	+	74%	Epistaxis		Right base	Pneumonectomy
Wodehouse[22]	19	M	0	0	0	0	0	0	0				Right base	Lobectomy
Wodehouse[22]	13	M	+	+	+	+	0	+	0		Headaches; blurred vision: convulsion		Right lower	Necropsy
Moyer and Ackerman[23]	29	M	0	0	0	0	0	0	0		Epistaxis; hematuria	Nevi over face, lips, tongue	Left lung	
Moyer and Ackerman[23]	26	M	+	+	+	+	0	0	+	63%	Dizziness; blurred vision	Lips, face, nose	Right lower	Pneumonectomy
Baer and co-workers	20	M	+	+	+	+	+	+	+	61%	Epistaxis; convulsions	Umbilicus	Bilateral	Lobectomies

At intervals during the next six years the patient underwent a series of venesections when his red blood count became too high, or the cyanosis too marked. At times the erythrocytes exceeded 8,000,000 per c. mm., and the hemoglobin reached 19 grams. He weathered a number of upper respiratory infections without difficulty. The bouts of epistaxis decreased, but effort dyspnea became a prominent symptom. Special note was made of the fact that despite reduction of the hemoglobin to 13 to 14 grams and the red cells to 4,700,000, the cyanosis was still present. The significance of this was not appreciated at that time.

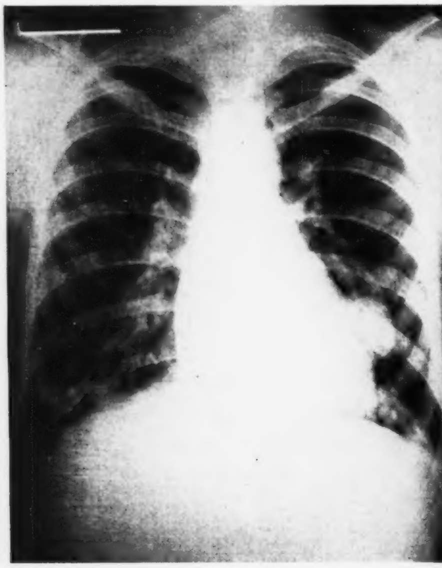

Fig. 1.—Roentgenogram, anteroposterior view, of the chest taken in November 1947. The nodular shadows in both lower lobes are readily seen.

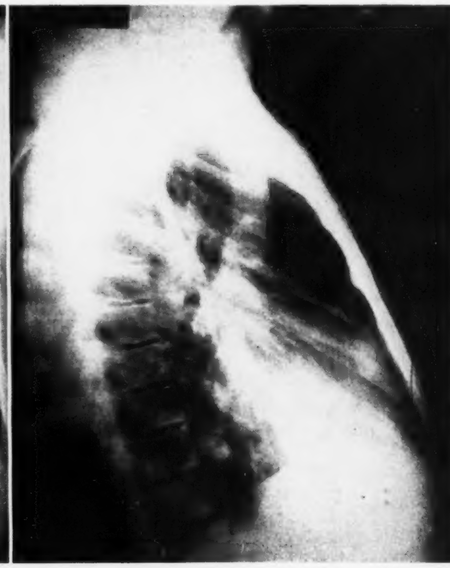

Fig. 2.—Roentgenogram, lateral view, taken in November 1947.

Table 2.—*Laboratory Data*

	11-20-47	11-25-47	12-30-47	1-5-48	1-12-48	1-20-48	4-22-48	5-10-48	12-15-48	12-27-48
Red blood cells (per cu. mm. blood)	4,900,000		6,850,000	6,600,000	5,960,000	5,570,000	7,500,000	6,000,000	5,650,000	
Hemoglobin (grams per 100 cc. blood)	13.0		11.5	12.0	10.8		16.7		13.2	14.7
White blood cells (per cu. mm. blood)	8,400		8,500	6,700					7,000	
Hematocrit	43%			54%	46%					
Blood sugar (mg. per 100 cc. blood)	99			143						
Blood urea (mg. per 100 cc. blood)	11			10						
Blood CO_2	58%	69%								
Prothrombin time	19 sec.									
Blood uric acid (mg. per 100 cc. blood)		5.7								

In May 1947, detailed hematologic studies were made, and the diagnosis of polycythemia vera seriously questioned. In October 1947 the patient had a profuse hemoptysis and x-ray study of the chest was advised. On photofluorography a diagnosis of ad-

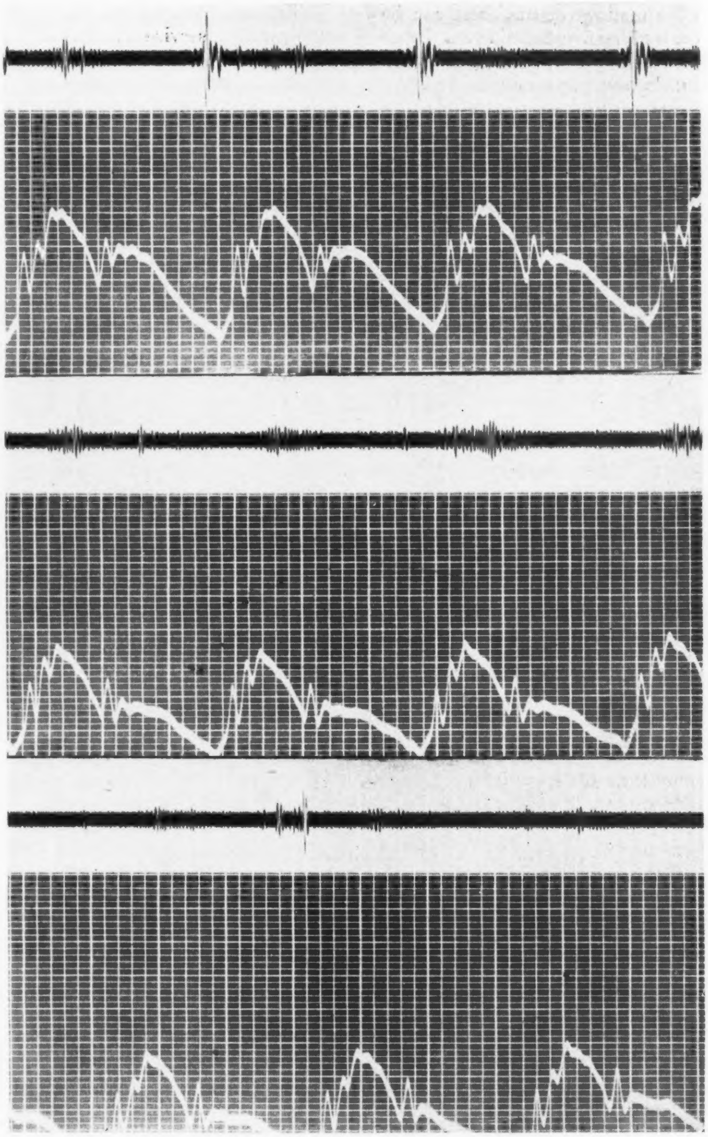

FIG. 3.—Simultaneous stethograms and carotid tracings made preoperatively. Lower curves in each record are carotid tracings. *A*, Stethographic record illustrating the late systolic murmur in the left axilla. *B*, Stethographic record taken in the right posterior thorax opposite the seventh dorsal spine, during inspiration. *C*, Tracing taken over the right posterior thorax, during expiration. Note the increase in intensity in the murmur.

vanced tuberculosis of both lower lobes was made. Sputum examinations showed no evidence of tuberculosis. On fluoroscopy, peculiar nodular opacities were noted in the right lower lobe and at the left border of the heart. A roentgen study of the chest was then made (figs. 1 and 2). The bizarre nodular opacities previously noted were seen. The radiologist concluded that "in view of the patient's history

of polycythemia, the findings in the chest can be explained on the basis of a polycythemia vera. Large nodular shadows in the lungs, as well as pulmonary vascular dilatation, do occur in this condition. We believe, however, that a diagnosis of multiple pulmonary cavernous angioma or arteriovenous fistula is more likely. Secondary polycythemia is part of the clinical syndrome of this disease. Angiocardiography could be used to prove the diagnosis." With this diagnosis in mind hospitalization was advised for confirmation and possible surgical therapy.

The patient was admitted to Jewish Hospital on the medical service of Dr. H. L. Goldburgh, on November 18, 1947. On admission, the cyanosis of the lips, fingers, and toenails was noted. There was obvious clubbing of the fingers and toes. By palpation and percussion, the heart was found to be slightly enlarged to the left; a faint mitral systolic bruit was audible. A few days after admission, bruits could be heard readily over the right base posteriorly and in the left axilla. These were not noted on thorough auscultation a few weeks previously. The

A

B

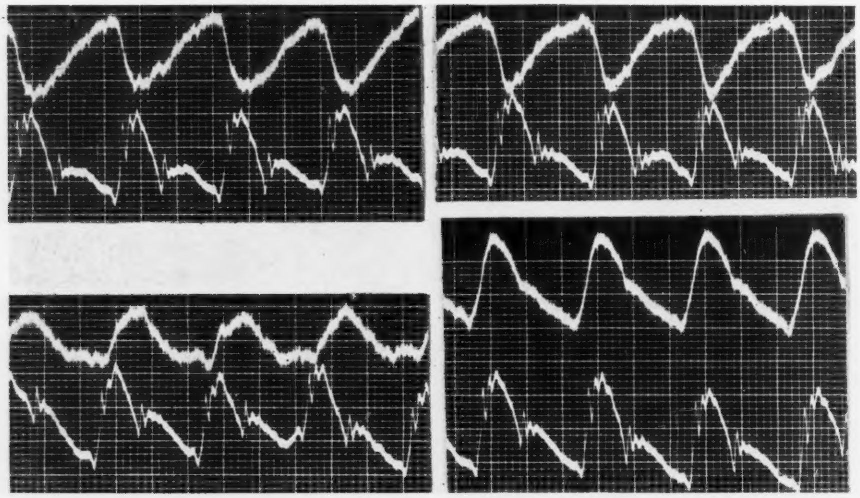

FIG. 4.—Electrokymograms and carotid tracings made preoperatively. Lower curves in each record are carotid tracings. *A*, Electrokymograms taken over the middle left border of the heart and the lesion in the left lung (posterio-anterior projection). The upper curve on the left is that of the middle border of the left ventricle. The upper curve on the right, which is quite similar, is that of the lesion in the left lung. *B*, Electrokymograms taken over the pulmonary artery (upper left) and the lesion in the right lower lung (upper right). The lesion in the lung showed an active movement of its borders corresponding to the arterial type of curve such as usually obtained over the pulmonary artery.

TABLE 3.—*Arterial Oxygen and Cardiac Output Studies*

	Normal Values	12-1-47	12-15-47	3-1-48	6-23-48	7-28-48	10-20-48	12-15-48	12-23-48	1-12-49	1-12-49*
Oxygen Content (vol. %)	19.6-21.2	9.7	9.0	12.9	14.7	13.1	11.2	12.5	15.6	15.85	17.7
Oxygen capacity (vol. %)	21.1-21.7	15.2	17.0	15.7	23.3	20.8	16.2	22.0	19.7	19.4	19.1
Oxygen saturation (%)	96-99	63.8	53.0	82.0	62.9	62.9	69.0	57.0	78.9	81.7	92.8
Hematocrit	about 45%			68.8%	66.6%	48.5%					55.5%
Cardiac output (liters/minute)		12.3		10.1	9.0		15.0	11.1			
Cardiac index (liters/minute/sq.m.)	2.2-6.0		7.0	6.0	5.7		9.5	6.7			

Right lower lobectomy on 1-6-48; left lower lobectomy on 5-12-48; left lingulectomy on 9-28-48.

Determinations made in the Department of Physiology, Temple University Medical School, except those of 12-23-48 and 1-12-49 which were made in the Pulmonary Function Section, Graduate School of Medicine, University of Pennsylvania.

* After inhalation of 100 per cent oxygen.

liver and spleen were not felt. The presence of moderate cardiac enlargement was demonstrated by both orthodiagram and x-ray study of the chest, as were the shadows and nodular opacities previously seen in the lower lung fields. Some of the laboratory findings at that time are tabulated in table 2. We again noted the presence of deep cyanosis despite a relatively normal blood count. Arm-to-lung and arm-to-tongue circulation times were normal. Attempts to delineate the pulmonary shadows by intravenous Diodrast were twice unsuccessful.

Synchronous sound and carotid tracings and roentgenkymograms gave further evidence that these pulmonary lesions were due to vascular abnormalities (figs. 3 and 4). Arterial oxygen determinations and cardiac output by the ballistocardiographic method were obtained (table 3, and fig. 5).

The various procedures performed were considered confirmatory of the diagnosis of bilateral arteriovenous fistulas of the lungs. The patient was discharged on December 4, 1947, with the understanding that surgery would be undertaken early in January 1948. Two weeks after leaving the hospital he had a number of severe hemoptyses, and he was readmitted December 29, 1947.

After the pulmonary bleeding subsided, lobectomy of the right lower lobe was performed on January 6, 1948. (Details of the surgical problems encountered in this and later operations are being reported elsewhere.[24]) At operation numerous dusky, pulsating vascular tumors were seen throughout the right lower lobe. The thrill felt on palpation disappeared upon compression or clamping of the pulmonary artery supplying the lower lobe. During the operation several large blood vessels were noted entering the inferior portion of the right lower lobe; these seemed to have penetrated the diaphragm.

Dissection of the lung specimen revealed marked dilation of the pulmonary artery and vein which had numerous large branches. These communicated

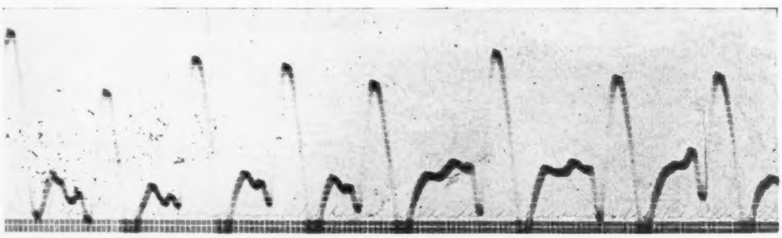

Fig. 5.—Ballistocardiogram taken on December 15, 1947 (30-gram weight calibration, Nickerson technic). Cardiac index averaged 7.0 liters per square meter per minute.

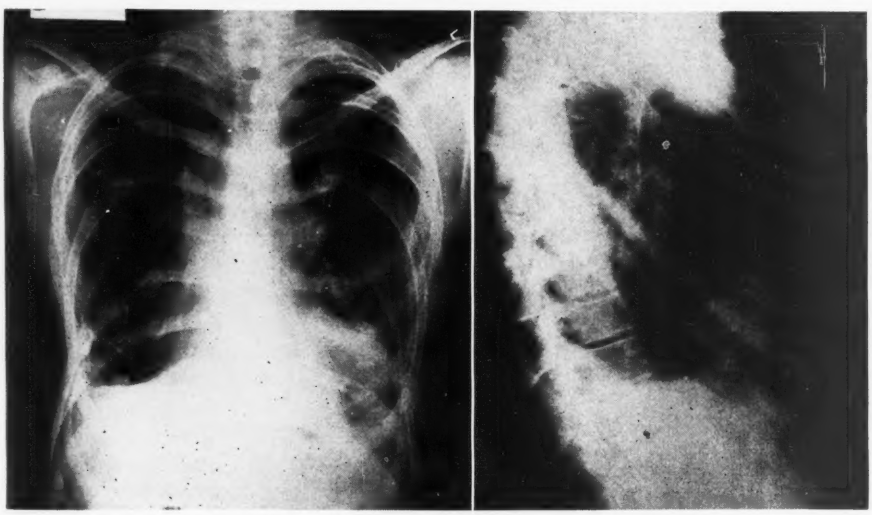

Fig. 6.—Roentgen-ray films taken in September 1948. Note the large A-V fistula in the lingual portion of the left upper lobe.

with a number of cystlike cavities 0.5 to 2.0 cm. in diameter. Each cyst communicated with two vessels, probably an artery and a vein. One could not always be certain of this, however, for even at the hilum there were so many vessels that veins and arteries could not be distinguished.

The patient did quite well postoperatively. Improvement was slow but continuous. Effort tolerance increased and the cyanosis became less, though it never completely disappeared. Repetition of the ballistocardiographic study showed a decrease in cardiac index to 6.0 liters per minutes. The preoperative oxygen saturation of 53 per cent rose to 82 per cent postoperatively, as seen in table 3.

factorily, and on May 12, 1948, lobectomy of the left lower lobe was performed. Study of the left lower lobe revealed a number of arteriovenous communications, varying in size and similar to those found in the right lower lobe. The postoperative course was uneventful; the patient was discharged in twelve days. However, it was observed during the next few weeks that the cyanosis had not disappeared, that the oxygen saturation had decreased to 62 per cent, and that the red cells rose to over 6,000,000 per cubic millimeter. A persistent tachycardia of 110 developed and deep cyanosis continued. It was felt that we were dealing with some postoperative pulmonary complication, or possibly

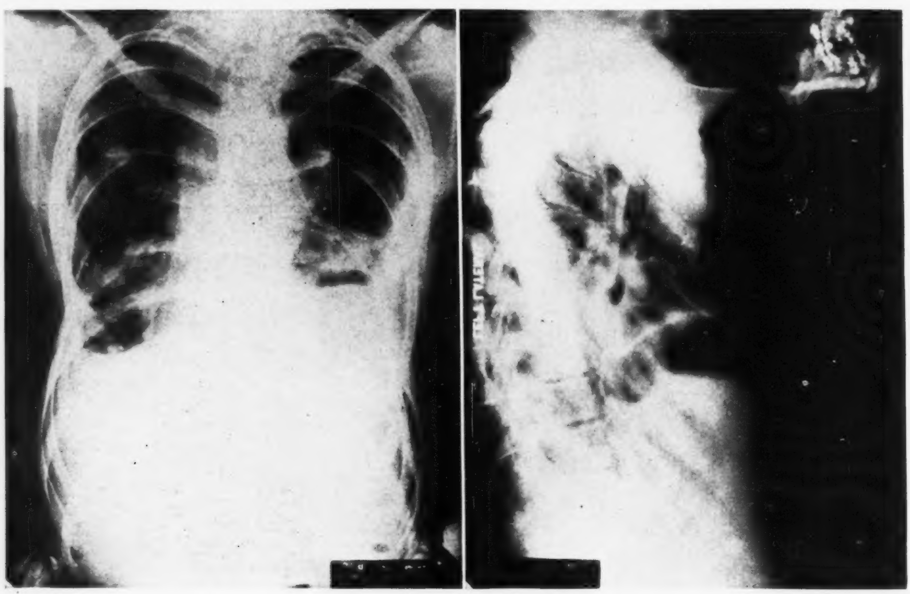

Fig. 7.—Roentgenograms of the chest taken postoperatively in November 1948.

The clinical condition having improved sufficiently, lobectomy of the left lower lobe was contemplated for the early part of May. On April 22 however, the patient suddenly had a convulsive seizure and lapsed into unconsciousness. He was aphasic upon admission to the hospital, and had a right sided hemiplegia. The Babinski sign was positive on the right. His condition appeared critical. The temperature rapidly rose to 103 F. and a blood count revealed 7,500,000 erythrocytes and 26,000 leukocytes per cubic millimeter, and 16.7 grams of hemoglobin per 100 cc. of blood. Following a phlebotomy of 500 cc. and left stellate ganglion block with 1 percent procaine hydrochloride, there was a marked improvement. The speech returned within forty-eight hours and the right-sided paralysis rapidly disappeared. Convalescence continued satis-

recurrence of the pulmonary arteriovenous communication. Roentgen-ray study in September revealed a large, circular, sharply demarcated shadow in the lower portion of the left upper lobe, overlying the left cardiac border (fig. 6). We then decided that we were faced with an expanded or new arteriovenous communication, which seemed much larger than any of those previously encountered. With a good deal of trepidation it was decided to attempt removal of this aneurysm. Anterior thoracotomy on September 28, 1948, revealed a large arteriovenous fistula involving the entire lingual portion of the left upper lobe, which was resected. Dissection of the specimen indicated it was larger than any individual fistula found in either of the lower lobes. The patient was discharged in relatively good condition on October 8, 1948 (fig. 7).

Discussion

Before considering the clinical features of this condition, it might not be amiss to discuss some of the congenital aspects of pulmonary arteriovenous fistulas. Most observers are in agreement with Wodehouse[22] who considered hemangiomas of the lung as "local manifestations of a generalized congenital tendency to maldevelopment of the blood vessels." It is more than just chance that in 50 per cent of the reported cases other vascular abnormalities, such as telangiectasias, capillary hemangiomas, and spider nevi, were exhibited. Rigid search will probably disclose other associated vascular anomalies in a high percentage of discovered cases. Moyer and Ackerman[23] have recently reported in detail two cases of familial telangiectasias with pulmonary involvement. They reviewed the question of hereditary familial telangiectasias, and pointed out the relationship of pulmonary hemangiomas to the generalized vascular disease. It is also true, however, that an occasional patient is seen in whom the pulmonary abnormality is the only vascular disturbance present.

The familial incidence of this disorder is worthy of comment. Goldman[8] in reporting one patient found a similar involvement in a brother, and bleeding tendencies in other members of the family. We have already referred to the report by Moyer and Ackerman[23] of 2 cases in brothers. In the discussion that followed Maier and collaborators'[21] presentation a number of discussers, in commenting on unreported cases they had seen, emphasized the familial aspects of the condition. While preparing the report on our patient, we noted that his father had a number of telangiectasias about the lips. Roentgen-ray study revealed nodular and cylindrical shadows in the lung fields that were quite suggestive of pulmonary hemangiomas.

Clinical Picture. The published reports of this disturbance emphasize the occurrence of the diagnostic triad—cyanosis, clubbing of the fingers and toes, and polycythemia. Cyanosis is usually the first finding, and was present in 21 of the 24 cases. Clubbing and polycythemia were found in 20 cases. All the manifestations of this clinical syndrome are physiologic responses to the anoxemia. A variable quantity of venous blood is shunted from pulmonary artery to vein without going through the pulmonary alveoli. As a result there is decreased oxygenation of the arterial blood, and a chain of compensatory mechanisms takes place. There is an increase in blood volume, as in all other arteriovenous fistulas. Burchell and Clagett[18] found it above normal in all of the 5 patients whose blood volume had been measured. Increase in hemoglobin concentration occurs and finally a rise in the number of circulating erythrocytes. The degree of oxygen unsaturation determines the compensatory hematologic mechanisms that are called into play. As the oxygen unsaturation and the polycythemia increase, cyanosis becomes more marked. Clubbing of the fingers and toes is undoubtedly a response to the oxygen unsaturation. Hemoptysis and cough occur as a result of oozing from or rupture of one of the aneurysms. It might be advisable at this point to emphasize the frequent occurrence of cerebral symptoms. Headache, dizziness, tinnitus, convulsive seizures, and hemiplegia have been reported in 50 per cent of the cases. The cerebral involvement may be extremely disturbing, as in our case. It is precisely these symptoms, together with the polycythemia, the epistaxis, the bleeding gums, and the corneal injection, that have led to the continued diagnosis of polycythemia vera. It seems logical to suggest that the oxygen unsaturation or the secondary polycythemia or both may be responsible for these cerebral manifestations, if we can exclude the possibility of intracranial vascular anomalies.

In addition to the cyanosis and clubbing of the fingers and toes, physical examination usually reveals pulmonary and cardiac murmurs. It is just this cyanosis, clubbing, and cardiac murmurs that so often leads to a diagnosis of congenital heart disease. Many observers[6, 10, 12, 13] have reported the presence of pulmonary bruits over the arteriovenous communications, as were found in our patient. Some have reported the murmur loudest at the height of inspiration,[10, 19] and others at expiration.[13] The murmurs and the thrill felt at operation disappeared with ligation of the abnormal vessels.

There is considerable disagreement concerning the cardiac abnormalities present. Kennedy, Burwell, and Sidney[25] have reported that peripheral arteriovenous fistulas produce an increase in cardiac work. If this continues long enough, cardiac hypertrophy and congestive failure develop. Most of the reports, however, suggest there is no cardiac disturbance present in these cases. Jones and Thompson[10] stated that "the lack of any cardiac hypertrophy or pathology is due to the fact that the arteriovenous fistula is confined to the pulmonary circuit." Smith and Horton,[6] Burchell and Claggett,[18] Bisgard,[19] and Moyer and Ackerman[23] all have subscribed to this view. Moyer and Ackerman[23] attributed the absence of cardiac enlargement (that usually accompanies peripheral arteriovenous fistulas) to low pressure in the pulmonary circuit. Maier and associates[21] stated that the cardiac output is normal.

We are not completely in accord with these views. The cardiac output in our patient was above normal, as was the frontal cardiac area. Wodehouse[22] has also reported a patient with cardiac enlargement. In our patient, there was a loud mitral systolic bruit that has decreased considerably since the last operation. The frontal cardiac area preoperatively (as determined by orthodiagram by two separate observers) was 30 per cent above the predicted normal. There has been decrease in the heart size since removal of the fistulas, so that the transverse diameter and frontal area are now within the predicted normal range. It is interesting to note that Burchell and Claggett's[18] patient also exhibited decrease in heart size following removal of the abnormal vascular communication. It is our feeling that the degree of cardiac hypertrophy depends on the degree of arteriovenous shunt, the increase in blood volume, and the amount of increase in cardiac work that results. Eventually, in all cases, some increase in heart size should be manifest, and a subsequent decrease following surgical extirpation of the fistulas.

Roentgen-Ray Findings. The radiologic findings in these cases are characteristic, and constantly present. They consist of one or more circular, cylindrical, or nodular lesions occurring in the lung fields. It will be recalled that Hirsch[26] originally reported nodular lesions in the lung fields occurring in polycythemia vera. It is quite possible that some of these shadows are due to arteriovenous fistulas, as suggested by Rodes.[5]

These pulmonary lesions are chronic and usually nonprogressive. They may pulsate, or there may be increased hilar pulsations on the side of the lesion. The determination of the number of fistulas present is important in any consideration of surgical treatment. It must be realized that the shadows demonstrated radiologically are usually the largest fistulas, but not necessarily the only ones. We have observed, as did Moyer and Ackerman,[23] that fairly large subpleural lesions may escape detection. In addition, small unsuspected lesions in one lobe may expand after removal of the larger fistulas in another lobe.

Special roentgen-ray technics have been used to delineate these pulmonary shadows more accurately. On planigraphic examination it is occasionally possible to trace some of the larger vessels as they arise from the hilum. Angiocardiographic studies have been successfully performed in a few cases, though our results with this procedure were not satisfactory. Good roentgenologic demonstrations of the lesions outlined with Diodrast have been published in conjunction with the case reports of Watson[20] and of Moyer and Ackerman.[23] Roentgenkymography may also help differentiate these lesions fron nonvascular shadows, as was done in our patient (see fig. 4).

Pathologic Findings. A number of the published reports have contained excellent discussions of the pathologic findings in the specimens obtained at operation or necropsy. We need not dwell on this phase of the problem at any length. It seems relatively academic whether these lesions are considered aneurysms or fistulas or hemangiomas. The degree of arteriovenous shunt determines the clinical abnormalities that occur. In some of the dissected specimens it has been possible to demonstrate the course and nature of the abnormal communications. In many, however, the number and degree of the anastamoses have been so great that satisfactory pathologic evaluation has been impossible.

Prognosis. It is generally agreed that serious or fatal hemoptysis will ensue if these pulmonary lesions are not treated surgically. Four patients have died from pulmonary hemorrhage. All those that have been operated upon have done well postoperatively, and maintained improvement as long as they have been followed after their surgery. An occasional patient, however, has refused surgery and apparently gotten along well. Some of the reported cases have been symptomatically negative and been discovered accidentally. The father of our patient, for example, is now 52 years of age, and has never consulted a physician because of a cardiac or pulmonary complaint. It seems logical to assume that the number and degree of arteriovenous communications will determine the symptomatology and the resultant treatment.

We have already referred to the cerebral and other associated complications of this condition. In one of Wodehouse's[22] cases a brain abscess occurred from which *Haemophilus influenza* was cultured. Death followed operation for the brain abscess. Maier and his associates[21] reported a case in which there was superimposed bacterial endocarditis. The patient responded to antibiotic therapy and was then successfully treated by lobectomy.

How well our patient will do is problematic. Since his discharge he has continued to gain weight and strength. His effort tolerance has improved, dyspnea is less, and cyanosis considerably decreased. The heart size has returned to normal and there is no polycythemia. The last x-ray examination of the chest (fig. 7) gave evidence that all the arteriovenous communications had been removed. The oxygen determinations, however, cast some doubt on this. The most recent arterial oxygen saturation still was only 81.7 per cent (table 3). Following inhalation of 100 per cent oxygen the saturation rose to 92.8 per cent, considerably less than the 99 per cent to 100 per cent saturation that should occur normally. According to Comroe[27] and others, this type of response is characteristic of an arteriovenous shunt. Continued observation will be necessary to determine the location of any remaining arteriovenous communications. It is possible that previously undetected fistulas in the upper lobes may eventually expand and become troublesome, with the changed pulmonary hemodynamics.*

Summary

1. Twenty-three cases of pulmonary arteriovenous fistulas have been reviewed, and an additional case in a man of 21 years reported in detail.
2. Some of the physiologic observations obtained have been presented.
3. The congenital and familial aspects of the condition are emphasized.
4. The clinical features of arteriovenous fistula have been discussed, as well as the resemblance to and differentiation from polycythemia vera and congenital heart disease.
5. We believe that this condition is not nearly as rare as considered, and that its clinical features should render its recognition easy.

Acknowledgments

The authors wish to express their sincere thanks to the U. S. Public Health Service at Temple University for taking the stethograms and roentgenkymograms, and to the Physiology Departments of Temple University and the Graduate School of Medicine, University of Pennsylvania, for the invaluable physiologic determinations.

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Spontaneous Rupture of a Peripheral Artery: Report of Case

By Albert A. Pollack, M.D., Edgar A. Hines, Jr., M.D., and Joseph M. Janes, M.D.

The case history of a patient with apparent spontaneous rupture of the posterior tibial artery is presented, with a brief review of the previously reported cases.

SPONTANEOUS rupture of a peripheral artery is a very rare condition. Bonnet, Martin, and Nikodievitch[1] reported 2 cases and found reference to one other case report in the literature. The first of their cases was that of a soldier 51 years of age who had typhus fever several weeks prior to the development of gangrene of the right lower extremity. Amputation was performed eleven days after gangrene was noted but the patient died shortly after operation. A postmortem examination revealed a rupture of the external iliac artery and vein. The second patient was a farmer 73 years of age who had had malaria and who shortly thereafter had experienced pain in the back of the right leg which soon began to swell and then became gangrenous. Amputation was performed and a rupture of the popliteal artery and vein was found.

A case of spontaneous rupture of the posterior tibial artery without apparent cause is reported herein.

Report of Case

A married white man, 38 years of age, in the wholesale grocery business, was admitted to the Mayo Clinic as an emergency patient on August 2, 1948.

The family history did not reveal that any member had suffered from a hemorrhagic disease or tendency. For sixteen years before coming to the clinic, the patient had noticed that he bruised easily, as a result of which small ecchymotic areas would develop on his body and especially on the lower extremities. Pain had developed four years previous to his registration but the calf of the right leg did not swell at that time. The pain had decreased rapidly upon elevation of the leg and the use of hot applications. Two years before he entered the clinic an episode of acute abdominal pain and distention had developed. Surgical exploration revealed hemoperitoneum but a bleeding point was not found. He had made an uneventful recovery after the operation.

Twelve days before admission a dull pain had developed in the right calf. The patient continued his work for the next three days. The pain became increasingly severe and while he was taking a hot bath he noted a rather sudden swelling of the right leg from the knee down. He was hospitalized in his home community the next day because of the pain and swelling, and shortly thereafter the involved leg became purple. The patient had been treated conservatively with elevation of the leg, rest in bed, and sedation but had continued on a downward course.

Careful and repeated questioning of the patient, his wife, and his brother on admission to the clinic and during his stay in the hospital failed to disclose any evidence of trauma to his leg.

Initial examination revealed a markedly asthenic, slightly icteric, and acutely ill man in great pain. The blood pressure reading was 135/100. Temperature, pulse, and respiration were normal. There were several small purpuric areas on the anterior thoracic wall, and the right leg was ecchymotic from 3 inches above the knee downward. There was no rigidity or tenderness of the abdomen. The liver, kidneys, and spleen could not be palpated. The lymph nodes in both inguinal regions were slightly enlarged. Results of rectal examination were negative. The peripheral arterial pulsations which are usually palpated were found to be normal. The right leg was moderately edematous and the skin was taut and warm. On palpation marked tenderness was noted in the calf of the right leg and the patient was unable to extend his leg. A soft systolic bruit was heard over the lower anterolateral aspect of the right leg.

The hemoglobin measured 9.5 grams per 100 cc. of blood, the erythrocytes numbered 2,600,000 per cu.mm., and the leukocytes 14,800 per cu.mm. of blood. Urinalysis revealed albuminuria, Grade 3.

Shortly after the initial examination the involved calf had increased 1.5 inches in diameter, and the pain also had increased. A diagnosis of active arterial bleeding was made, and immediate surgical intervention was considered necessary.

Arteriography was performed in the operating room with 25 cc. of a 35 per cent solution of diodrast injected into the right femoral artery; the posterior

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tibial artery could be visualized only for about 1.5 inches from its origin. The artery was then exposed and found to have two perforations about 1.5 inches distal to the bifurcation of the popliteal artery. The posterior tibial artery was ligated and the involved section of the artery was removed and sent to the pathology laboratory for study. A hematoma of clotted and nonclotted blood was evacuated. An apparent cause for the perforations was not found at the time of the operation but it was noted that both arteries and veins in this region were very friable.

Morphologic study of the section of artery revealed an acute polymorphonuclear leukocytic exudation around the point of rupture but the arterial wall was damaged to such an extent that definite changes could not be visualized.

With the evacuation of the hematoma and ligation of the artery, there was relief of pain. Further studies were then carried out in an attempt to discover the cause of this condition.

Results of serologic examination were negative. The bleeding time was three minutes; the blood coagulation time (Lee-White method) was six minutes and thirty seconds. The prothrombin time (Quick method) was twenty-eight seconds; large doses of synthetic vitamin K were administered intravenously after operation and the prothrombin time returned to a normal of twenty seconds. The platelet count was 130,000 per cu.mm. of blood and the level of ascorbic acid in the blood was 0.3 mg. per 100 cc. of plasma.

The fat content of the blood was within the normal range as was the urea content. The direct reaction for serum bilirubin (van den Bergh test) was negative and the indirect reaction disclosed 1.5 mg. of bilirubin per 100 cc. of serum one day after operation. This returned to normal before the patient was dismissed from the hospital. No sulfobromophthalein (bromsulfalein) was retained at the end of one hour. The sedimentation rate of erythrocytes was 30 mm. in one hour.

Study of special blood smears revealed hypochromasia with polychromatophilia and a differential count of 13 per cent lymphocytes, 7 per cent monocytes, and 80 per cent polymorphonuclear leukocytes; 69 per cent of the leukocytes were filament cells and 11 per cent were nonfilament cells. Sternal biopsy revealed normal bone marrow cells. The only abnormality indicated in a roentgenogram of the thorax was an elevation of the right side of the diaphragm.

After transfusion of blood and just prior to the patient's dismissal from the hospital, the hemoglobin measured 12.2 grams, and the erythrocytes numbered 4,600,000 per cu.mm. of blood and the leukocytes 7,700. The results of urinalysis were negative.

A section of the left ulnar artery that was removed and studied, was found to be normal. The patient made an uneventful recovery and was dismissed from the clinic on August 23, 1948.

The case reported is interesting in that a cause for the rupture of the artery was not apparent. Herrman[2] reported a case of rupture of the deep epigastric artery and explained the rupture on the basis of the anatomic structure of the musculature of the abdominal wall. However, Bonnet, Martin, and Nikodievitch,[1] who were unable to study the walls of the vessels at the point of rupture because of the condition of the specimens, studied the proximal portions of the vessels and concluded that there were two predisposing causes for rupture: (1) an atheroma involving the media of the artery and (2) the previous existence of a severe infection. They felt that the infection became localized in the atheroma and thus weakened the wall of the artery sufficiently to permit rupture. The extravasated blood caused periphlebitis and phlebitis in the contiguous veins.

Our patient did not give a history of localized trauma or previous infection and we did not discover a focus of infection. Atheromas were not present in the sections of artery that were studied. The possibility of localized arteritis or a small aneurysm at the point of rupture was not excluded but the presence of either seems unlikely.

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ABSTRACTS

BACTERIAL ENDOCARDITIS

Mair, J., and O'Hara, M. M.: Subacute Bacterial Endocarditis in Pregnancy. J. Obst. & Gynec. Brit. Emp. **56**: 652 (Aug.), 1949.

A successfully treated case of subacute bacterial endocarditis arising during pregnancy is described. A total of 151 million units of penicillin was given over a period of almost three months, treatment being discontinued four weeks after parturition. Delivery was successfully accomplished with the aid of low forceps under low spinal anesthesia.

One of the problems which must be faced in the management of such cases is whether or not the pregnancy should be terminated. This question must be answered on the basis of both the functional cardiac classification of the patient and the stage to which pregnancy has advanced. Since further valvular damage may occur even during therapy, it would seem best to terminate an early pregnancy as soon as the disease is under control. Since the cardiac load shows a considerable rise about the twentieth to twenty-fourth week, it would seem advisable to terminate pregnancy well before the twentieth week. However, after the twentieth week artificial termination of pregnancy is a dangerous procedure in patients with cardiac disease, and it is better to avoid surgical interference at this time. Such patients do better when allowed to go into labor spontaneously and delivered vaginally, often with the assistance of forceps.

SCHWARTZ

Hurst, W. W., Gleason, A. L., and Schemm, F. R.: Subacute Bacterial Endocarditis after Operation for Tetralogy of Fallot. Northwest Med. **48**: 763 (Nov.) 1949.

The authors report a case in which subacute bacterial endocarditis developed after operation for tetralogy of Fallot. At the age of 8, following anastamosis of the proximal end of the right carotid artery to the right side of the pulmonary artery, the patient improved. When 10 years old, she was admitted to hospital with a clinical picture of subacute bacterial endocarditis. Blood cultures were positive for *Streptococcus viridans*. With penicillin therapy the temperature fell to normal after the fourth day of this treatment. The signs and symptoms of congestive failure, apparent on admission, cleared rapidly with digitalization, moderate sodium restriction and fluids ad libitum.

BELLET

BLOOD COAGULATION

Fisher, B.: The Effect of Several Diluents on Prothrombin Activity Curves. Brit. J. Exper. Path. **30**: 352 (Aug.), 1949.

The author reports a study of the effect of several different diluents for plasma in the preparation of prothrombin activity curves. Dilutions of the normal oxalated dog plasma were made with each diluent, in the order of 100, 70, 50, 40, 30, 20 and 10 per cent.

The essential change produced by serial dilution of normal plasma was a reduction in the amount of prothrombin present. Distilled water, 0.9 per cent saline solution and protein-free filtrate of normal serum produced uniformly similar results as diluents, duplicating the characteristic hyperbolic curve. Prothrombin-free (adsorbed) plasmas were found to be sources of error if a good preparation was not made. Normal serum could not be used as a diluent because of the presence of small amounts of prothrombin, fibrinogen and activator substances.

BELLET

Thuerer, G. R., and Angevine, D. M.: Influence of Dicumarol on Streptococcic Infection in Rabbits. Arch. Path. **48**: 274 (Sept.), 1949.

Following the work of Menkin, indicating the importance of fibrin in localizing infection due to staphylococci and pneumococci, the authors studied fibrin formation in dicumarolized rabbits and its effect on experimentally-induced streptococcic dermatitis. Seven of 13 rabbits that responded to the drug with a prolonged prothrombin time had positive cultures, and 5 of them died from bacteremia. Less fibrin was found in the skin of dicumarolized animals than in comparable untreated control animals. The authors suggest that the lack of fibrin in tissues of treated animals was probably a factor in the spread of the infection, in contrast to localization of infection in control animals.

GOULEY

Stats, D., and Davison, S.: The Increased Hypoprothrombinemic Effect of a Small Dose of Dicumarol in Congestive Heart Failure. Am. J. M. Sc. **218**: 318 (Sept.), 1949.

The hypoprothrombinemic effect of a single dose of 150 mg. of dicumarol was determined in 48 control subjects and in 36 patients with varying degrees of right-sided cardiac failure. Clinical and statistical analysis of the results showed an increased response in those cardiac patients with moderate to severe failure. It is recommended that when dicumarol is administered to patients with cardiac failure for the treatment of thromboembolic conditions, doses smaller than those recommended for the average patient should be administered.

DURANT

Litwins, J., Vesell, H., Kissin, M., Cohen, I., and Paul, A.: Effect of Dicumarol on the Erythrocyte Sedimentation Rate. J.A.M.A. **141**: 330 (Oct. 1), 1949.

Dicumerol was given to 12 persons with normal sedimentation rates, to 14 patients with myocardial infarction and elevated sedimentation rates, and to 8 patients with medical conditions other than myocardial infarction who had elevated sedimentation rates. No change in the sedimentation rate attributable to the administration of dicumerol in therapeutic doses was noted.

HANNO

Silverman, S. B.: Changes in the Coagulability of the Blood after Radiation Therapy. Am. J. Roentgenol. **62**: 541 (Oct.), 1949.

Frequently repeated determinations of blood coagulation were determined in a group of patients being treated for neoplastic diseases. The coagulation time was performed under controlled conditions in tubes containing increasing amounts of heparin. Coagulation time was plotted against heparin concentration (Waugh-Ruddick test). Blood coagulability was found to be decreased. This trend was roughly proportional to the total irradiation received.

Possible causes of this change are reviewed. The author believes that the effect was not on prothrombin formation but rather on the platelets and thromboplastin.

SCHWEDEL

CONGENITAL ANOMALIES

Swan, C.: Rubella in Pregnancy as an Aetiological Factor in Congenital Malformation. Stillborn, Miscarriage and Abortion. Part II. J. Obst. & Gynec. Brit. Emp. **56**: 591 (Aug.), 1949.

On the available evidence, a woman who contracts rubella at some stage during the first four months of pregnancy has a three to one chance of giving birth to a congenitally defective infant. After the fourth month the risk of congenital malformation is minimal. The main malformations are varying degrees of cataract, deaf-mutism, heart disease and microcephaly. Each may occur alone or in any combination. In addition, intrauterine death may possibly follow rubella in pregnancy. The critical period for the development of congenital cardiac defects is from the fifth to the eighth week of intrauterine life, during which time the septa are forming, the bulbus cordis is undergoing involution, and torsion of the great vessels is taking place. It is the relatively low virulence of the virus of rubella which enables the embryo, though damaged, to survive. The question of whether other virus diseases may be followed by congenital malformations remains open.

Prevention of rubella infection during pregnancy can be accomplished by prophylactic active immunization with the virus before the childbearing period and possibly by the use of convalescent serum and gamma globulin soon after contact with rubella. On the available evidence, utilization of therapeutic abortion if rubella is contracted during the first four months of gestation appears to be justified.

SCHWARTZ

Benham, G. H. H.: Pregnancy and Coarctation of the Aorta. J. Obst. & Gynec. Brit. Emp. **56**: 606 (Aug.), 1949.

The author analyzes 53 cases of coarctation of the aorta in pregnant women reported in the literature, and presents 3 additional cases. In the previously recorded cases, 6 patients died during pregnancy, labor or puerperium; pregnancy precipitated or aggravated cardiovascular symptoms in 11 cases; and in the remaining 36 pregnancy apparently had no injurious effect on the cardiovascular system. Two of the reported deaths were attributable to the precipitation of cardiac failure by the additional cardiovascular demands of pregnancy. Three of the deaths were due to aortic rupture, and 1 to cerebral hemorrhage. Since arterial rupture was the cause of 4 of the 6 reported deaths, its prevention must be the specific aim of good management. Although this risk cannot be entirely eliminated, it should be greatly diminished if material rise in arterial tension could be avoided. Nearly all observers agree that there is a sustained blood pressure rise during labor. Instrumental delivery and vaginal manipulation may cause a rise of as much as 50 mm. These facts indicate that the ideal method of delivery in cases of coarctation of the aorta is one which eliminates labor and also avoids obstetrical manipulations through the vagina. These conditions are best satisfied by performing caesarean section at term before the onset of labor. Present information does not justify prohibition of, or interruption of pregnancy in patients without symptoms or with minimal intolerance to effort, provided that expert prenatal care is available.

SCHWARTZ

Shapiro, M. J.: Diagnosis of Congenital Heart Disease by Ordinary Methods. Radiology **53**: 469 (Oct.), 1949.

The author states that in operating on more than 100 patients with patent ductus arteriosus, several with coarctation of the aorta and about 60 with cyanotic congenital heart disease, he has had only one error in diagnosis. None of the patients were studied with refined aids, such as angiocardiography or cardiac catheterization. He presents a resumé of the clinical and significant roentgenographic findings in subaortic stenosis, coarctation of the aorta, patent interventricular septum, patent ductus arteriosus, dextrocardia, tetralogy of Fallot, Eisenmenger's complex, pulmonary stenosis, tricuspid atresia, transposition of greater vessels, and truncus arteriosus.

SCHWEDEL

Dadds, J. H. and Hoyle, C.: Congenital Aortic Septal Defect. Brit. Heart. J. **11:** 390 (Oct.), 1949.

The authors report an instance of proved congenital aortic septal defect, review the pertinent data on 10 previously reported cases and discuss the diagnosis of this lesion.

The findings in the presented case and a review of findings in previously reported cases indicate that the average age of death is 14 years; cardiac insufficiency dates from early infancy; the basic murmurs are those of a free leak from the aorta above the cusps; the heart is always much enlarged; other congenital cardiovascular lesions are usually absent; the pulmonary arterial tree is dilated.

This defect must be differentiated from (1) patent ductus arteriosus which is usually but not always possible. In the latter anomaly the heart and pulmonary vessels are not so strikingly enlarged and the murmur is not as superficial in character. (2) Atrial septal defect should be distinguishable because it does not produce excessive aortic pulsations nor an increased pulse pressure and gives characteristic findings on right heart catheterization. (3) In atrial septal defect combined with a patent ductus arteriosus, right heart catheterization will also be conclusive. (4) In truncus communis which produces cyanosis early, a systolic murmur and thrill are usually present. The main pulmonary artery and branches are rudimentary or absent.

SOLOFF

Chapman, D. W., Earle, D. M., Gugle, L. J., Huggins, R. A., Zimdahl, W.: Intravenous Catheterization of the Heart in Suspected Congenital Heart Disease. Arch. Int. Med. **84:** 640 (Oct.), 1949.

Intravenous catheterization of the heart in 72 cases of suspected congenital heart disease is discussed. The method and the application of the procedure to the more accurate diagnosis and the study of the disturbed physiology of congenital heart disease are presented with a notation of the complications that may be encountered. The results of this method in sixty-nine cases are given, and several detailed case reports representative of the acyanotic, potentially cyanotic, and cyanotic types of heart disease, as well as of pulmonary arteriovenous aneurysm and dilated pulmonary artery with hypoplastic aorta, are given.

BERNSTEIN

Neuhauser, E. B. D.: Tracheo-Esophageal Constriction Produced by Right Aortic Arch and Left Ligamentum Arteriosum. Am. J. Roentgenol. **62:** 493 (Oct.), 1949.

One of the causes of tracheoesophageal constriction by a vascular ring is the passing of a ligamentum arteriosum from a right aortic arch to the left pulmonary artery. Disability is characterized by dysphagia especially for solid foods, wheezing, stridor, and repeated respiratory infections including pneumonia.

Five patients who exhibited these symptoms are presented. On conventional radiographic examination there was indentation of the esophagus from the right in the posteroanterior view. In the left anterior oblique position there was a small indentation of the esophagus from behind due to the ligamentum arteriosum. The effects of vascular constriction on the trachea were demonstrated with the aid of lipiodol within the trachea. However, these were less striking than the effects upon the esophagus. Surgical exploration and division of the ligamentum arteriosum freed the vascular constriction and offered complete relief in all instances.

SCHWEDEL

Hertzman, V. O., and Strong, G. F.: Patent Ductus Arteriosus. Canad. M. A. J. **61:** 495 (Nov.), 1949.

The authors present a study of 18 patients, 17 of whom were explored surgically because of a tentative diagnosis of patent ductus arteriosus, and one of whom died of subacute bacterial endarteritis without surgical intervention. In 11 cases, a ductus was found, ligated and divided. In 6 cases the preoperative diagnosis was in error.

The authors state that in patent ductus arteriosus the typical murmur is continuous or machinery-like, with a systolic accentuation, and best heard in the second left intercostal space close to the sternum. The systolic component is frequently heard widely over the precordium and between the scapulae, and is often transmitted into the neck vessels and left axilla. In this series, a "typical" continuous murmur was present in 9 of 12 cases of patent ductus and was found in 2 cases in whom there was no functioning ductus at operation. A typical thrill was found in all except one of the proved cases in the group; it was also found in 4 patients who did not have a patent ductus on exploration. Certain factors, such as infancy, other congenital anomalies, subacute bacterial endarteritis and congestive failure may complicate the clinical picture.

BELLET

Wright, C. J. E.: Coarctation of the Aorta with Death From Rupture of a Cerebral Aneurysm. Arch. Path. **48**: 382 (Nov.), 1949.

The author reports a case of coarctation of the aorta associated with congenital bicuspid aortic valve with death from rupture of a cerebral aneurysm. The victim was a young woman aged 19, who had been in good health. Death followed the sudden onset of headache and vomiting. Neck rigidity, blood-stained spinal fluid, and the presence of a diastolic aortic murmur constituted the important physical signs. Necropsy revealed atheromatous streaking in the ascending aorta and particularly in the common carotid arteries, in marked contrast to its absence below the coarctation. A small aneurysm in the left anterior cerebral artery was the site of hemorrhage.

The author reviews the frequence of these associated lesions and reports the surprising information that only 16 such cases have been recorded. He comments on the excellent health experienced by most of these patients. However, an abnormally high blood pressure was present in the upper extremities in every case.

GOULEY

CONGESTIVE HEART FAILURE

Schumann, H.: The Mechanism of the Therapeutic Effect of Digitalis or Strophanthin in Heart Failure. Ztschr. f. Kreislaufforsch. **38**: 606 (Oct.), 1949.

Heart failure with dilatation of the right heart was produced in white rats by intravenous injection (0.05—0.1 cc.) of mercury. At necropsy the content of glycogen and lactic acid in the heart muscle was determined by means of a very rapid preparation technic. Compared with controls, animals in heart failure had an increased amount of lactic acid and a decreased glycogen content in the heart muscle. If treated by digitalis, a reverse change occurred although values found in the normal control animals were not reached. The author's conclusions are that the therapeutic effect of digitalis is based upon an increase of oxidative metabolic processes in the failing heart, which works partly under anaerobic conditions. No increase of efficiency by digitalis can occur in the normal heart, where aerobic processes are already of optimal degree.

PICK

Levy, M. N., Berne, R. M.: Production of Acute Experimental Circulatory Failure by Graded Pulmonary Artery Constriction. Proc. Soc. Exper. Biol. & Med. **72**: 147 (Oct.), 1949.

The authors employed a graded pulmonary artery stenosis to produce experimental circulatory failure. Optically recorded pressure pulses from the aorta, pulmonary artery, and right atrium showed that judicious compression of the pulmonary artery could reduce the output of the left ventricle significantly without causing a drastic fall in the arterial pressure. This graded pulmonary artery constriction also resulted in a reduction of pulmonary systolic and diastolic pressure distal to the constriction and the development of a systolic murmur. It also produced a rise in maximal and initial pressures in the right ventricle and an increase in the right atrial tension. In some instances a relative tricuspid insufficiency developed. The elevation in central venous pressure was associated with a shift of a large volume of blood to the venous side of the circulation. Evidence was presented that a part of this shift occurred from the pulmonary vascular bed, although it was admitted that a shift might also occur within the systemic circuit itself toward the central veins.

MINTZ

Schneierson, S. J., and Bergman, H.: Mercurial Diuretics and Urinary Retention. J.A.M.A. **141**: 382 (Oct. 8), 1949.

Five cases of acute urinary retention in middle-aged and elderly men treated with mercurial diuretics for congestive heart failure are reported. In patients with prostatic enlargement and partial obstruction, the profound diuresis occasioned by the use of a mercurial diuretic may result in overdistention of the bladder and impairment of the bladder's motor function.

HANNO

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Mills, G. Y., Simon, A. J., Cisneros, F., and Katz, L. N.: Myocardial Infarction. Observations on 100 Patients Who Survived up to Six Years. Arch. Int. Med. **84**: 632 (Oct.), 1949.

One hundred patients who had survived one to six years after an acute myocardial infarction were examined. Seventy-seven of these 100 patients showed little electrocardiographic restitution, 14 showed partial restitution and 9 showed complete restitution.

Heart failure appeared almost entirely in the group of patients with little electrocardiographic restitution, but the electrocardiographic pattern after infarction did not prognosticate survival of the patient. The occurrence of clinical angina in 39 of 91 patients whose condition was electrocardiographically diagnosed as chronic coronary insufficiency (little or partial restitution) indicated the frequency of the association of clinical angina with the electrocardiographic pattern of chronic coronary insufficiency in patients surviving myocardial infarction.

BERNSTEIN

Sussman, M. L., Dack, S. and Paley, D.: Some Clinical Application of Electrokymography: The Findings in Myocardial Infarction and Heart Block. Radiology **53**: 500 (Oct.), 1949.

Electrokymographic studies in three instances of myocardial infarction involving the lower portions of the left ventricle indicated delayed systolic contraction, expansion instead of inward retraction in systole, and paradoxical inward movement of the affected portions during the rapid inflow phase in diastole.

Electrokymographic studies in two cases with complete heart block indicated simultaneous auricular motion over both atria and increased amplitude of atrial contraction in late systole. The authors demonstrated systolic accentuation of the heart sounds (bruit de cannon) when the interval between auricular and ventricular contractions was slight, and they discuss these in relation to increased tension of the A-V valves, and to the amplitude of ventricular systolic pulsations.

SCHWEDEL

Hecht, H. H.: Concepts of Myocardial Ischemia. Arch. Int. Med. **84:** 711 (Nov.), 1949.

Many factors upset the balance between oxygen supply and work requirements of the heart muscle. This results in general or local myocardial ischemia. The syndrome of myocardial ischemia is characterized by pain, electrocardiographic changes and certain remote reactions secondary to tissue destruction. The electrocardiographic changes are manifold. They are determined by the intensity of the process and by the location of the lesion with respect to the recording electrodes. "Delay of repolarization" involves the T wave proper; "incomplete repolarization" (with flow of resting currents during diastole) modifies the RS-T segment. The direction of the changes with respect to the isoelectric base line of the electrocardiogram is determined by the location of the predominantly ischemic region. "Subendocardial" and "subepicardial" involvement may thus be contrasted.

In myocardial infarction, the signs of gross tissue destruction are added to those of myocardial ischemia. It is therefore suggested that the term "myocardial ischemia without tissue destruction" be used to define angina pectoris and "myocardial ischemia with tissue destruction" to denote myocardial infarction.

The "point of tolerance" defines the limits of cardiac reserve. In decompensated ischemia, the signs and symptoms appear when the patient is at rest. If an appreciable cardiac reserve is still available, an objective diagnosis can only be made by appropriate functional tests. Alterations in the electrocardiogram during the functional test in patients who have suffered an episode of myocardial infarction depend largely on the degree of revascularization. The result of the test in such patients may allow certain limited prognostic conclusions.

Myocardial ischemia from any cause tends to improve spontaneously in many instances.

BERNSTEIN

ELECTROCARDIOGRAPHY

Laake, H.: On Supraventricular Extrasystoles. Acta med. Scandinav. **134:** 23 (May), 1949.

The author reviewed the electrocardiograms of 12,473 hospital patients and made a statistical analysis of the extrasystoles noted in the records. Extrasystoles were found in the records of 286 patients (2.3 per cent). Ventricular extrasystoles were found in 181 cases (1.5 per cent) and supraventricular extrasystoles in 105 cases (0.8 per cent). The latter group included 3 patients who had both ventricular and supraventricular extrasystoles at the same time. The frequency of extrasystoles increased with age; this increase was found to begin at the age of 20 in cases with ventricular extrasystoles, whereas the number of cases of supraventricular extrasystoles in this study remained approximately constant up to the age of 50 years.

Other electrocardiographic abnormalities were noted in 80 per cent of the patients with supraventricular extrasystoles and in 61.3 per cent of those with ventricular extrasystoles. Abnormal P waves were found in 47.6 per cent of tracings showing supraventricular extrasystoles. Measurement of 85 tracings with supraventricular extrasystoles showed a compensatory pause in 15. There was evidence of organic heart disease in 64.7 per cent of the patients with supraventricular extrasystoles, and in 50.8 per cent of the patients with ventricular extrasystoles.

SCHWARTZ

Moll, A., and Korth, C.: The Influence of the Position of the Heart on the Electrocardiogram in Prevalent Hypertrophy of the Left Heart. Ztschr. f. Kreislaufforsch. **38:** 351 (June), 1949.

Different patterns of left ventricular hypertrophy in the standard limb leads are explained by the help of aV unipolar limb leads, V chest leads and a lead from the gastric cavity (V_G). These additional leads are noncontributory if the heart is in the horizontal position, but are of great diagnostic value if the heart is in vertical position. A rare pattern of left axis shift in the standard lead with a nonspecific low T_1 or inverted T_2 and inverted T_3 may be seen with forward rotation of the apex along the transverse axis. Here the diaphragmatic leads (V_G and aV_F) face parts of the right ventricular surface as well as parts of the hypertrophied left ventricle. A similar summation of potentials of right and left ventricle may be observed in posterolateral infarction with the heart in horizontal position where the T-wave inversion shows up in Leads II and III, V_{4-6}, and aV_F, but not in aV_L. Such mixed potentials in the chest leads may be indicated not only by a transitional QRS complex, but also by QRS followed by an inverted T wave over the right side of the chest, similar to that seen in left sided hypertrophy over the left side.

PICK

Unghvary, L.: Electrocardiographic Diagnosis of Coronary Venous Disturbances. Cuore e circolaz., **33**: 146 (June), 1949.

Coronary venous stasis, produced in the dog by ligation of the coronary sinus, was followed by electrocardiographic changes, the most typical being low voltage of QRS and T waves. This "pathological low voltage" was a reversible pattern since the electrocardiogram returned to normal after removal of the ligation. This finding was considered by the author to be just as distinctive of venous stasis as the infarction pattern is typical of arterial ischemia. According to the author, low voltage in clinical tracings may be due to venous stasis, either alone or combined with other factors.

LUISADA

Rawkind, M.D., and Lonstam, G. L. S.: Complete Heart-Block Associated with Amoebic Hepatitis. Lancet **257**: 152 (July 23), 1949.

The authors report a case of amoebic hepatitis in a patient 28 years of age whose presenting symptoms were pain and fainting episodes which proved to be Stokes-Adams attacks. Diarrhea, which had recurred intermittently in the past, rapidly responded to emetine. Clinical and roentgen study suggested the presence of amebic hepatitis with inflammatory changes spreading through the diaphragm into the lung. The heart was enlarged and the electrocardiogram between Stokes-Adams seizures revealed complete A-V heart-block. The heart block disappeared and the Stokes-Adams attacks ceased shortly after the start of therapy with emetine. The authors postulate that the cardiac lesion was due to blood-borne amebic metastases.

In three previously reported cases of amebiasis with auriculoventricular dissociation the patients had diarrhea. This and other features of the disease thus introduced other possible factors which might affect the conduction tissues. Among these mentioned are anemia, toxemia, malnutrition, peripheral circulatory failure, uremia, and abnormal blood and tissue chemistry.

BELLET

Malinow, M. R., Moia, B. and Battle, F. F.: Action of Potassium on Pathological Electrocardiograms. Rev. argent. de cardiol. **16**: 226 (July–Aug.), 1949.

The electrocardiographic changes induced by the oral administration of 10–20 Gm. of potassium chloride were analyzed in a group of 50 patients with normal and abnormal electrocardiograms. No significant changes in cardiac rate or auriculoventricular conduction were found. The Q-T interval was shortened in many cases. The variations observed in the ventricular complex did not confirm the conclusions of previous authors who have claimed that potassium chloride might be useful for the differentiation between "primary" and "secondary" changes of the T wave. The suggestion is made that hyperpotassemia at nontoxic levels causes alterations of the T wave by accelerating, in variable degree, epicardial repolarization, both in normal and pathologic hearts.

LUISADA

Braun, K., Stuczynski, L. A., and Grossowicz, N.: Electrocardiographic Changes Produced on the Syrian Hamster (Cricetus Auratus) by Diphtherial Toxins. Proc. Soc. Exper. Biol. & Med. **72**: 58 (Oct.), 1949.

Diphtherial toxins exposed to alkaline reactions and administered to the golden hamster produced, in addition to neurotoxic symptoms, marked disturbances in heart function as evidenced by electrocardiographic changes. The electrocardiographic abnormalities consisted of ectopic beats, and partial and complete auriculo-ventricular block. Acid-treated toxins did not cause any electrocardiographic changes. The electrocardiographic changes frequently preceded the paralytic symptoms and, when sublethal doses were administered, the electrocardiogram remained abnormal even after the neurologic symptoms had disappeared. It is concluded that electrocardiographic examination of heart function seems to be a more sensitive method of measuring the action of certain diphtherial toxins than the observation of the neurotoxic symptoms.

MINTZ

Wallace, L., and Clark, E.: Electrocardiographic Changes in a Case of Wernicke's Syndrome. Ann. Int. Med. **31**: 675 (Oct.), 1949.

A 40 year old chronic alcoholic, exhibiting mental confusion, diplopia, horizontal nystagmus and loss of the deep tendon reflexes in the lower extremities, was diagnosed as a case of Wernicke's syndrome (hemorrhagic superior polioencephalitis). Neurologic response to an intensive course of thiamin was fairly prompt. During the first four days of the patient's hospitalization, a moderately elevated temperature was present. Electrocardiograms made during this febrile period were abnormal in that the T waves in standard limb Leads II and III were inverted. These deflections were normal in electrocardiograms made on the sixth and twentieth days of his hospitalization. Associated with this reversion to a normal pattern, there was a slowing of the sinus rate. Enlargement of the heart was not shown by the x-ray film of the chest. The temporary T-wave abnormalities were assumed by the authors to be an electrocardiographic expression of vitamin B deficiency.

WENDKOS.

Abrahams, D. G.: The Q-T Interval in Acute Rheumatic Carditis. Brit. Heart J. **11**: 342 (Oct.), 1949.

The purpose of this investigation was to determine whether prolongation of the Q-T interval was a reliable index of active carditis and whether this finding had prognostic significance. Of 134 patients studied, 100 had active carditis. Of the patients with

activity, 55 made an uninterrupted recovery and 45 had prolonged activity. Twelve patients had inactive carditis and 22 had no carditis. Bazett's formula and Ashman and Hull's criteria for the corrected Q-T interval were used. The upper limit of normal for Q-Tc was accepted as 0.422 second for men and children and 0.432 second for women.

Ninety per cent of those with active carditis had prolonged corrected Q-T intervals. Five of the 12 with presumably inactive carditis had prolonged corrected Q-T intervals. These 5 were proved by subsequent manifestations to have had active carditis; the authors therefore believed that the other 7 might have had otherwise unrecognized active carditis. The corrected Q-T interval was below the upper limits of normal in all 11 instances of active rheumatic fever without carditis.

Both digitalis and pericarditis shortened the Q-T interval and at times prevented the appearance of a prolonged corrected Q-T interval in active carditis. On the other hand, ventricular hypertrophy alone without active carditis at times caused a prolonged corrected Q-T interval.

Relapses of active carditis were characterized by prolongation of the corrected Q-T interval. This measurement may be used as a guide to physical activity. However, with the present data, it does not seem justifiable to enforce long periods of bed rest when a long corrected Q-T interval is the only abnormal finding.

SOLOFF

Klein, H. A., and Myers, G. B.: The Diagnostic Value of High Precordial Leads. J. Lab. & Clin. Med. **34:** 1618 (Nov.), 1949.

High precordial leads taken at the intersections of vertical lines through the V_3, V_4, V_5 and V_6 positions with a horizontal line at the junction of the third interspace and sternum have been obtained on approximately 4,000 patients. The findings in these leads were correlated with those in the customary precordial and Goldberger limb leads and with the pathologic findings in 300 cases that came to autopsy.

Cardiac rotation appeared to have a greater influence on the QRS pattern in high precordial leads than in those taken in the usual positions. Clockwise rotation displaced the transitional zone farther to the left in high than in the customary precordial leads and often led to the registration of an RS pattern, typical of the potential variations of the epicardial surface of the right ventricle, in leads high in the axilla as well as in aV_L. Counterclockwise rotation tended to shift the transitional zone farther to the right in the high than in the routine precordial leads.

High precordial leads were of particular value in the detection of infarcts localized to the basal portion of the anterior or lateral walls of the left ventricle, as demonstrated by pathologically proved cases with diagnostic signs in high precordial leads but not in the routine precordial or limb leads.

High precordial leads were also of value in the estimation of the basilar extent of anterior or lateral apical infarcts, as illustrated by cases of localized anterolateral apical infarction, showing diagnostic patterns in the customary but not in the high precordial leads and extensive anterolateral infarction with diagnostic patterns at both levels. The differentiation from high precordial lead patterns due to right and left ventricular hypertrophy and right and left bundle branch block is illustrated.

AUTHORS

HYPERTENSION

de Takats, G.: The Corticoadrenal Factor in Hypertension. Surgery **26:** 67 (July), 1949.

The author studied a group of hypertensive patients, preliminary to sympathectomy, in regard to their corticoadrenal function, in an attempt to elucidate the problem of failure of such an operation in individuals preoperatively considered to be appropriate candidates for it. An insulin tolerance test, consisting of a three-hour study of the effect of an intravenous injection of insulin upon the blood sugar, was performed upon all 50 patients in the series. Eight patients demonstrated an abnormal response in the form of an absence of the drop in blood sugar. This group, which was considered to be insulin resistant, was subjected to an intravenous sugar tolerance test. On the basis of the results, it was suggested that corticoadrenal activity might be a factor at least in some cases of hypertension.

ABRAMSON

Leathem, A.: The Retinal Vessels in Hypertension. Quart. J. Med. **18:** 203 (July), 1949.

After studying the optic fundi of 111 patients with varying degrees of hypertension and of 103 normal subjects, the authors reached certain conclusions. They feel that hypertension can be diagnosed with reasonable certainty by opthalmoscopic fundings alone (1) if either of the following findings are present, namely irregularity of the lumen in at least two arterioles, or the lumen of one arteriole less than one-half the width of its companion vein, with less than the normal 2:3 ratio between most of the others; (2) if two of the following three changes are present, namely, pallor of the arteriolar blood column, changes at the arteriovenous crossings, and a broad or bright light reflex.

In patients with high diastolic pressures (110 mm. Hg or more), 10 per cent had normal retinal vessels, while 89 per cent had hypertensive retinal arterioles, 89 per cent showed left ventricular enlargement by fluoroscopy, and 69 per cent revealed left ventricular preponderance by electrocardiography. In patients with a low diastolic pressure (90 mm. Hg or less) but a systolic pressure of 160

mm. Hg or more, hypertensive retinal arterioles were found in 50 per cent, left ventricular enlargement in 44 per cent, and left ventricular preponderance in 25 per cent. Of the entire series of hypertensive patients (111), 70 per cent had retinal arteriole changes which were never found in the control series; 66 per cent had enlargement of the left ventricle; and 50 per cent showed left ventricular preponderance.

The author suggests that in cases of cardiac enlargement of unknown etiology with normal or equivocal blood pressure, examination of the retinal vessels should be of help in determining whether hypertension is the cause.

MARGOLIES

Heller, E. M.: The Treatment of Essential Hypertension. Canad. M. A. J. **61**: 293 (Sept.), 1949.

The author describes what he believes to be the proper treatment for essential hypertension. Hypertension is divided into two groups; systolic hypertension, and diastolic hypertension. Essential hypertension is the form of hypertension in over 70 per cent of the cases classified as diastolic hypertension. Correct diagnosis is therefore important in order to rule out the nonessential types of high blood pressure.

The proper therapy includes rest, sedation, psychotherapy, and reduction of weight. Obesity is usually an associated etiologic factor only; nevertheless, the blood pressure drops significantly and even becomes normal, and remains so if weight is kept within normal limits. Sodium restriction therapy by means of two different types of diets often results in improvement even in cases of advanced hypertension. As regards sympathectomy, the author feels that the most opportune time for operation is in a patient under 50 years of age, who has been observed regularly and whose hypertension and symptoms and signs are persisting and progressing in spite of adequate conservative therapy.

The author reports the success of a low sodium diet in the treatment of a series of 5 cases, 4 of whom had previously failed to respond to other conservative therapy.

BELLET

Owens, F. M.: Relief of Chronic Hypertension by Excision of Pheochromocytoma. Arch. Surg. **59**: 896 (Oct.), 1949.

The author reports a case of chronic hypertension caused by pheochromocytoma and cured by the removal of the tumor. This patient had been advised to undergo sympathectomy; during the process of study for renovascular diseases the patient was admitted to the hospital because of suspected appendicitis. This disease was not present but a mass was felt in the midepigastrium which proved to be a pheochromocytoma. The author concludes that both adrenal regions should be explored routinely at the time of sympathectomy for hypertension. The tumor, however, may not lie in the adrenal regions but may arise wherever chromaffin tissue is found. Tests for epinephine-producing tumors are simple and can be utilized to advantage in the study of the hypertensive patient.

BECK

Vakil, R. L.: A Clinical Trial of Rauwolfia Serpentina in Essential Hypertension. Brit. Heart J. **11**: 350 (Oct.), 1949.

Rauwolfia serpentina, a large climbing or twining herb or shrub, belonging to the natural order Apocynaceoe, has been extensively used in India, with apparent success, as a remedy for hypertension. This drug is said to act on the vasomotor center, leading to generalized vasodilation with lowering of the blood pressure; to depress the cerebral centers with soothing of the general nervous system; to produce a sedative action on the gastric mucosa; to produce a stimulating action on the intestinal smooth muscle; and to stimulate the bronchial musculature.

The author studied the effect of this drug on the blood pressure of 50 hypertensive patients. In 73 per cent of cases there was a drop of both systolic and diastolic blood pressure after one week of therapy. After four weeks of therapy, 62 per cent of cases developed a "moderate" or "marked" drop of both systolic and diastolic pressure levels. The systolic drop varied from 2 to 54 mm. with an average of 21 mm. The diastolic pressure showed a drop of 4 to 34 mm. with an average drop of 11 mm. The blood pressure lowering effect of the drug could be reproduced by a second administration.

The author states that the drug was essentially nontoxic, but occasionally individuals complained of drowsiness, depression, diarrhea, anorexia, nausea, vomiting, vertigo, giddiness, polyurea, nocturia and abdominal pain.

SOLOFF

PATHOLOGIC PHYSIOLOGY

Segall, H. N., Wener, J., and Druckman, R.: Carotid Sinus and Coronary Circulation. Canad. M. A. J. **61**: 118 (Aug.), 1949.

The authors examined an unselected group of controls, subjects who had no clinical evidence of coronary artery disease, and a group of patients who had cardiac pain and other evidence of coronary artery disease. Carotid sinus pressure was applied to both groups; the duration and intensity of the pressure was varied to avoid producing loss of consciousness in those with a sensitive carotid sinus, and to elicit a maximum effect in those with an insensitive carotid sinus.

No cardiac pain occurred in their series of 416 patients as the result of carotid sinus pressure. About one-third of the cases developed prolongation of the P-R interval. Pressure on the left as well

as the right side of the neck was equally effective in prolonging the P-R interval. Carotid sinus pressure elicited both auricular and ventricular premature ectopic beats in a small number of cases. Carotid sinus pressure did produce some abnormality of the T wave without the development of pain in nineteen instances. Abnormalities in T waves were produced only in patients with striking clinical evidence of impairment in coronary circu'ation, both in terms of cardiac pain on exertion and electrocardiographic abnormalities indicating myocardial fibrosis, the result of coronary occlusion in the past.

It is postulated that carotid sinus pressure resulted in the production of sufficient acetylcholine in these few cases to elicit abnormalities of T waves similar to those produced in dogs and in man by the intravenous or subcutaneous administration of acetylcholine or by prolonged vagus stimulation.

BELLET

PATHOLOGY

Rinehart, J. F., and Greenberg, L. D.: Effect of Experimental Thiamine Deficiency on the Heart of the Rhesus Monkey. Arch. Path. **48:** 89 (July), 1949.

The authors studied the problem of cardiac involvement in isolated experimental thiamine deficiency in monkeys. Seven animals were subjected to varying degrees of thiamine dietary depletion, being under observation for periods of fifty days up to one hundred and seventy days. Three of these 7 animals were subjected to two episodes of acute depletion, 2 others to three such episodes; one animal received repeated suboptimal doses of thiamine, while the last animal was examined after a single depletion period of fifty days' duration.

The authors point out that animals subjected to such depletion will not show any changes for three weeks, and the pathologic observations made at such a time will show nothing of note. However, after prolonged and recurring periods of depletion, as carried out in this study, a definite cardiac pathology is manifest in rhesus monkeys. Gross examination of the hearts of these 7 animals revealed dilatation of the right auricle and ventricle and occasionally left ventricular dilatation.

Significant microscopic findings were noted in 4 of the 7 animals. These were of two types: One was focal necrosis of the heart muscle of variable extent, apparently a slow degeneration of individual muscle fibers rather than an acute massive necrosis. The other cardiac lesion was seen in the same 4 animals. It consisted of swelling and development of large clear areas in the cytoplasm of subendocardial muscle fibers accompanied by hypertrophy and hyperchromatism of the muscle nuclei. There was usually some interstitial edema. This microscopic lesion was most frequently seen in the left ventricle, but was also present in the right. The size and distribution of these involved fibers indicate that they are part of the conduction system. These changes are not seen in the auricles.

The authors state that necrosis of the myocardium has been noted in swine, in pigeons, in dogs, foxes, and recently in rats. They believe that hydropic degeneration of the fibers of the conduction system is probably distinctive of thiamine deficiency. They quote Wenckebach as having observed an identical pathologic change in his classic study of the beriberi heart in man. They admit that hydropic degeneration of the myocardium can be seen in conditions other than thiamine deficiency.

GOULEY

Barker, W. F.: Syphilitic Aortitis with Obstruction of Multiple Aortic Ostia. New England J. Med. **241:** 524 (Oct. 6), 1949.

The author reports a case with one of the more unusual cardiovascular complications of syphilis. A 52 year old man was admitted to the hospital complaining of severe pain in the anterior part of the chest radiating down the left arm. Electrocardiograms were considered suggestive of infarction of the anterolateral aspect of the left ventricle with subendocardial extension. Three hours after admission the patient died suddenly. The clinical diagnosis was coronary thrombosis with myocardial infarction and syphilis with suspected aortitis involving the coronary ostia. Necropsy revealed syphilitic aortitis and endarteritis in which there was obliteration of the lumen of the innominate artery, partial obstruction to the lumen of the left subclavian artery and almost complete occlusion of the coronary ostia. The diagnosis of coronary-ostia disease should be more readily suspected when, in association with electrocardiographic changes of "global ischemia," there is evidence of other ostial obstruction, with or without a demonstrable aortic aneurysm.

BELLET

Shucksmith, H. S., and Macpherson, I.: Dissecting Aneurysm of the Aorta. Brit. M. J., **4634:** 963 (Oct. 29), 1949.

During the course of a fatal case of dissecting aneurysm, the presence of an embolism near the aortic bifurcation was suspected. Marked spasm of the arteries of the lower limb with coldness and paralysis of the limbs was noted. The initial physical findings suggested embolism completely blocking the right common iliac artery and partially blocking the left. The symptoms, however, occurred earlier in the left limb than in the right, making the diagnosis of embolism unlikely. Rapid and marked improvement of the limb occurred shortly after the onset. The last portion of the skin to become warm following recovery was a localized area above the ankle. The authors suggest that there may be an exceptional vascular arrangement at this site and

that this may be related to the common occurrence of ulcers at this location.

TANDOWSKY

Conston, A. S.: Healed Dissecting Aneurysm. Arch. Path. **48**: 309 (Oct.), 1949.

Conston reports a case of healed dissecting aneurysm which, from clinical data, was apparently of only twenty months' duration. The interesting features were (1) a "double-barreled" aorta, extending from the beginning of the thoracic aorta down to the bifurcation, with re-entrance into the left iliac artery; (2) the emergence of the intercostal arteries from the new channel; (3) the origin of the left renal artery from the new vessel at the same level as that of the right artery, which came from the old channel; (4) the normal appearance of the left renal artery throughout its length with excellent preservation of the left kidney; (5) the atheromatous deposit in both aortas, more so in the new channel.

The patient was a 58 year old man with advanced hypertensive disease who twenty months before death had had his first episode of illness, an attack of severe epigastric pain. Laboratory and x-ray studies of kidney function revealed a normal status.

The author comments on the scarcity of similar cases of dissecting aneurism in which paired visceral arteries (renal or spermatic) have different origins in "double-barrelled" aortas.

GOULEY

Schlicter, J. G., Amromin, G. D., and Solway, A. J. L.: Dissecting Aneurysms of the Aorta. Arch. Int. Med. **84**: 558 (Oct.), 1949.

In an attempt to ascertain the underlying etiologic factors in dissecting aneurysm of the aorta, fourteen consecutive instances of dissecting aneurysm of aorta were reviewed from the clinical and morphologic point of view; eleven were reviewed with emphasis on changes in the vasa vasorum.

The most frequently demonstrable pathologic alterations found in aortas with dissecting aneurysms are medionecrosis, undermined arteriosclerotic ulcers, and rarely, syphilitic lesions. It appears that anoxia of the vascular wall is apparently the most important factor in the development of medionecrosis. Such anoxia may develop as a result of various factors: (1) Occlusive diseases of the vasa vasorum secondary to arteriosclerosis, arteriolosclerosis or other alterations of the hyperplastic variety. (2) Alterations in the hemodynamics of the vasa vasorum (dilatation with resultant stasis of blood may explain dissecting aneurysm first becoming manifest after shock or severe infections in man). (3) Diminished oxygen saturation of the blood or severe anemia (when combined with another mechanism). (4) Congenital abnormalities in the distribution of the vasa vasorum or paucity of collateral circulation through the adventitia or the outer third of the media.

Two of the cases reviewed by the authors were due to arteriosclerosis and 12 were secondary to medionecrosis of the aorta. Alterations were encountered in the vasa vasorum of nine aortas; seven of the nine showed associated medionecrosis of the aorta.

BERNSTEIN

Finestone, A. J., and Geschickter, C. F.: Bone Formation in the Heart. Am. J. Clin. Path. **19**: 974 (Oct.), 1949.

A 63 year old Negro man with a clinical diagnosis of pulmonary tuberculosis expired on the sixth day after hospital admission. At autopsy a hard, calcific mass was found in the lateral wall of the right ventricle, the medial aspect of which was incompletely covered by myocardium and endocardium. Examination of the myocardial mass showed a rim of relatively normal appearing cardiac muscle surrounding a definite layer of dense hyaline connective tissue which was undergoing calcification. The central area of the mass was composed of a meshwork of collagenous connective tissue and bone spicules.

The authors believe that the mechanism in all dystrophic calcification and ossification, regardless of site, is similar. They state that a diminished blood supply for any reason, plus the other necessary requisities, will produce calcification. If an increased vascularity occurs later, ossification may result.

BELLET

Barach, J. H.: Arteriosclerosis and Diabetes. Am. J. Med. **7**: 617 (Nov.), 1949.

The author reviews some of the known facts concerned in the etiology and pathogenesis of arteriosclerosis. It is pointed out that all types of arteriosclerosis (atherosclerosis, Moenckeberg's medial sclerosis, and arteriolar sclerosis) occur much earlier and more extensively in diabetics than in nondiabetics.

From the etiologic point of view, there is evidence that dietary, endocrine, mechanical, and hereditary factors are of importance. Knowledge concerning the relative roles of exogenous and endogenous cholesterol in the development of arteriosclerosis is at present incomplete, but tracer studies may cast some light on the problem.

Specific measures for the prevention and treatment of arteriosclerosis must await further clarification of the etiologic and pathogenetic mechanisms involved. At the present time, reduction in weight of the obese and restriction in the amount of animal fat in the diet seem to be of value.

HANNO

Wipf, H., and Brawner, H.: Cardiac Hypertrophy in Experimental Arteriovenous Fistula. Arch. Path. **48**: 405, (Nov.), 1949.

The authors produced experimental arteriovenous fistulas in large dogs by joining the common carotid

artery and the external jugular vein. The communication was large, postoperative thrombosis was prevented, and the animals were maintained from sixty-seven up to one hundred and five days. A surprising result was the absence of hypertrophy and (collaterally) a lack of increase in weight in the hearts of these dogs. This was in sharp contrast to the results of the same procedure in rabbits where the increase in cardiac weight varied from 45 to 125 per cent. The authors conclude that dogs may compensate for the additional circulatory load more efficiently than rabbits.

GOULEY

PHARMACOLOGY

Bülbring, E., and Burn, J. H.: Action of Acetylcholine on Rabbit Auricles in Relation to Acetylcholine Synthesis. J. Physiol. **108:** 508 (June), 1949.

Recent work has suggested that acetylcholine is not only a humoral transmitter of vagal impulses but also plays an important part in spontaneous contraction of the heart. Freshly excised rabbit auricles in Tyrode's solution will beat for a twenty-four to thirty-six hour period. Acetylcholine added to the solution depressed the beat. When the auricles have ceased beating they can be restarted by acetylcholine; a further addition of acetylcholine may increase the rate and amplitude.

When freshly excised auricles were made into a powder and incubated they synthesized acetylcholine at the average rate of 40 μg. per gram of powder per 75 minutes. Powder made from auricles which had stopped beating synthesized only about 15 μg. per gram of powder per 75 minutes. The synthesis of acetylcholine, therefore, is closely related to spontaneous activity of cardiac muscle.

Acetylcholine inhibited auricular contractions when this synthesis was proceeding at a high rate; and stimulated contraction when applied to auricles in which its synthesis was proceeding at a slow rate. In short, when the auricular beat stops and the synthesizing power rapidly declines, the addition of acetylcholine restores the beat and augments the synthesizing power. This supports the view that the activity of the heart and the synthesis of acetylcholine are inseparably linked.

WAIFE

Watkinson, G.: Massive Salicylate Therapy in Rheumatic Fever. Ann. Rheumat. Dis. **8:** 120 (June), 1949.

In the present survey, 80 service patients suffering from rheumatic fever were treated with a minimal dose of aspirin (not exceeding 100 grains daily), a moderate dose (200 grains daily with and without 100 grains of sodium bicarbonate daily), and a massive dose (from 120 grains to 600 grains daily) to maintain blood salicylate levels above 30 mg. per cent. The drug had to be given every four hours in order to maintain effective salicylate levels.

Alkalis accelerated the urinary excretion of salicylates. Dehydration caused a rapid increase in serum concentration. Variation in daily excretion was also caused by alteration of urinary pH, a deterioration in mixtures of salicylate solution and crystalline salicylate in the dispensing mixtures used, and the tolerance that developed after prolonged administration.

The massive dose therapy was most effective in rapidly lowering the temperature to normal, shortening the duration of symptoms, and returning the sedimentation rate to normal. The moderate dose schedule was more effective than the minimal dose. No reduction in relapse rate or in the incidence of carditis was seen. Toxic effects were greatest and most frequent with the massive dosage schedule.

LECKS

Hayes, D. W., Wakim, K. G., Horton, B. T. and Peters, G. A.: The Effects of Dihydroergocornine on the Circulation in the Extremities of Man. J. Clin. Investigation **28:** 615 (July), 1949.

Dihydroergocornine (DHO-180), an alkaloid derived from ergot, was administered intravenously to 20 subjects. The peripheral blood flow was determined by the venous occlusion plethysmograph with a compensating spirometer recorder.

There was an increase in peripheral blood flow which varied with the method of injection and the extremities. An average increase of 117 per cent (range 35 per cent to 214 per cent) was noted in the arms of 6 persons when dihydroergocornine was given by infusion. The average increase was 78 per cent in the lower extremities. When the drug was given by a single intravenous injection, the average increase in blood flow was 84 per cent and 63 per cent for the upper and lower extremities, respectively. The overall average for the entire group were 94 per cent in the upper and 68 per cent in the lower limbs. No significant changes in blood pressure were found in normotensive subjects but the pressure did fall in 2 hypertensive patients. A moderate reduction in heart rate was found. Side reactions were observed in all but one case. Nasal congestion producing severe obstructions of the passages was the most common complaint. Nausea, headaches, and flushing were also noted.

WAIFE

Tichy, V. L., and Zankel, H. T.: Prevention of Venous Thrombosis and Embolism by Electrical Stimulation of Calf Muscles. Arch. Phys. Med.**0:** 711 **3** (Nov.), 1949.

By means of electrodes placed around the legs, the authors studied the effect of artificially produced rhythmic contractions of the calf muscles on the prevention of postoperative intravascular clotting. Six hundred thirty-nine patients were subjected to this

type of therapy, and one of this group developed venous thrombosis after operation. In the opinion of the authors this was much less than would have been anticipated in a comparable control group.

ABRAMSON

Ellis, S.: The Action of Sympathomimetic Amines on the Isolated Heart of the Frog. J. Pharmacol. & Exper. Therap. **96**: 365 (Aug.), 1949.

This paper concerns the chemical nature of substances possessing sympathomimetic action on the heart. The author tested a large number of arylalkylamines and aliphaticamines on the isolated heart of the frog. The following observations were made: (1) The isolated frog's heart shows epinephrine-like responses to 2-phenylethylamine derivative with at least one hydroxyl group in either the 3- or 4- position on the ring. Compounds with secondary (methyl- or isopropylamino) or tertiary amine groups are also active. (2) When the side chain is lengthened to three carbon atoms, only 3, 4-dihydroxyphenyl compounds are active. ζ-dihydroxyphenylalanine (DOPA) produces positive inotropic effects. (3) The aliphatic sympathomimetic amines produce positive inotropic changes which are reversible only with difficulty. Certain characteristics of the actions of these compounds indicate that the mechanism of action differs from that of epinephrine. (4) Phenyl- and cyclohexyl- alkylamines do not possess positive inotropic activity. (5) Ergot alkaloids, Priscol, 2-(piperidinomothyl)—6-methoxy tetralone and dibenamine are unsatisfactory adrenolytic agents when applied to the frog's heart.

GODFREY

Carr, C. J., Burgison, R. N., Vitcha, J. F., and Krantz, J. C., Jr.: Anesthesia, XXXIV. Chemical Constitution of Hydrocarbons and Cardiac Automaticity. J. Pharmacol. & Exper. Therap. **97**: 15 (Sept.) 1949.

Cyclopropane-epinephrine induced ventricular arrhythmia is a well known phenomenon and may be reproduced by a wide variety of substances other than cyclopropane or chloroform. The substances known to reproduce this effect include many anesthetic agents in use today. The eleven cyclic and acyclic hydrocarbons, when inhaled, sensitize the myocardium to epinephrine while the aliphatic ethers as a class do not. However, ethylene, an unsaturated hydrocarbon, has been found to be without sensitizing effect on the myocardium; thus it acts more like an aliphatic ether.

In an attempt to correlate chemical structure with sensitizing effects, the authors chose several other unsaturated hydrocarbons. Sensitization appeared to be lessened with the presence of unsaturation in the molecule; however, the failure to sensitize was a matter of degree and not dependent upon the absolute absence of some sensitizing chemical structure.

GODFREY

Stark, W., and Barrera, S. E.: Use of Potassium in Protracted Insulin Coma: Preliminary Report. Arch. Neurol. & Psychiat. **62**: 280 (Sept.), 1949.

The purpose of this paper is to add 2 cases to the reported instances of protracted insulin coma and to present a relatively new mode of therapy. The diagnosis of protracted insulin coma in the 2 reported cases was made when the patients failed to recover from coma following the administration of what was thought to be adequate amounts of dextrose (each patient received a minimum of 125 Gm. intravenously in a 25 per cent solution). This led the authors to conclude that disturbed carbohydrate metabolism was not the sole factor in producing protracted coma.

The response following the administration of potassium was dramatic. The patient rapidly emerged from the comatose state. The authors administered potassium in a 1 cc. tuberculin syringe. Since discernible cardiac changes (lowering of cardiac rate with alteration in rhythm and transient electrocardiographic changes) occurred during the course of administration of potassium, the heart was constantly auscultated during administration of the drug, and a second injection was not given until normal cardiac rhythm was established. Using a 10 per cent solution, the material was injected very slowly at the rate of 0.02 to 0.04 Gm. at a given injection. By this method of administering potassium, critical concentrations were rarely reached.

The authors do not attribute the therapeutic responses obtained solely to the use of potassium nor do they feel that a direct correlation between the response and the drug exists. As yet, the nature of the initiated changes remains a problem for study. They state that this is the first known report of a case of protracted coma in which the patient was treated by the intravenous administration of potassium.

BELLET

Halbeisen, William A., Gruber, Charles M. Jr., and Gruber, Charles M.: A Study on the Comparative Depressant Effects of Hypnotic Drugs (Medomin, Seconal and Phenobarbital) on Heart Muscle and Cardiac Vagus Nerve. Anesthesiology **10**: 585 (Sept.), 1949.

The authors report the results of an investigation carried out on hearts of frogs to determine whether cycloheptenylethyl barbiturate (Medomin) is free of cardiac effects, and upon terrapins (Chrysemys marginata) to determine whether it has a depressant action on the cardiac vagus nerve similar to that produced by all other barbiturates. In order to compare the activity of this barbiturate with that of other barbiturates, similar molecular concentrations of Seconal sodium and phenobarbital sodium were studied on the same hearts

Cycloheptenylethyl barbiturate, like other barbiturates, when added to the perfusate caused a

decrease in the height of the contractions of the perfused isolated frog heart. In many experiments it also decreased the rate of heart beat. The authors' results indicate that approximately twice the molecular concentration of phenobarbital sodium is required to produce the same depression as is produced by cycloheptenylethyl barbiturate and that twice the concentration of this barbiturate is required to produce the same degree of depression as is produced by Seconal sodium.

In the experiment on the cardiac vagus nerve in the turtle, cycloheptenylethyl barbiturate again appeared to be approximately twice as depressant as phenobarbital sodium, whereas Seconal sodium appeared to be twice as active as cycloheptenylethyl barbiturate.

BELLET

Swan, H. J. C.: Effect of Noradrenaline on the Human Circulation. Lancet **257:** 508 (Sept. 17), 1949.

The author reports on the effect of noradrenaline on the human circulation. The subjects of the experiment were normal healthy men between 20 to 30 years of age. An intravenous infusion of 0.06 mg. of l-noradrenaline per minute for four minutes was given to each.

The effect on the blood pressure was a rise to hypertension levels, with both systolic and diastolic pressure levels well above basal values. The average rise in systolic pressure during the period of maximum effect was from 120 to 160 mm. of mercury. A bradycardia was also a pronounced feature. The rise in diastolic pressure that occurred in the presence of a bradycardia suggested an increase in total peripheral resistance. The infusion of noradrenaline in the blood flow through the hand, which is chiefly through skin, resulted in a definite vasoconstriction which was maintained during the period of infusion.

BELLET

Rogers, M. P.: Priscoline and Arteriosclerotic Peripheral Vascular Disease. Geriatrics **4:** 315 (Sept.–Oct.), 1949.

The author discusses the effect of Priscoline, 25 mg. three to five times daily, on fifteen geriatric patients with obliterative arterial disease. In every case there was a definite, measurable improvement; the average oscillometric increase in the right leg was from 3.3 mm. to 5.15 mm. and in the left leg from 2.75 mm. to 3.7 mm. Priscoline, however, is not without its disadvantages. In cases of arteriosclerosis associated with moderate to severe coronary insufficiency and in cases of marked hypertension, Priscoline (in a dose of 25 mg.) may produce some acceleration of the heart and a moderate increase in systolic blood pressure. Therefore, in such cases, it is suggested that smaller doses of the drug be used.

BELLET

Last, J. H., Rodriguez, A., and Pitesky, I.: Effect of Adrenergic Blocking Agents on the Cutaneous Action of Epinephrine. Proc. Soc. Exper. Biol. & Med. **72:** 119 (Oct.), 1949.

The adrenergic blocking agents used in this study were N-(2-chloroethyl)-dibenzylamine hydrochloride (Dibenamine) and N-(2-bromoethyl)-N-1-naphthalene-methylamine hydrobomide (SY-28). These agents were administered by direct diffusion or by ion transfer through the skin in order to avoid the generalized toxic manifestations encountered when given by the parenteral route.

Both Dibenamine and SY-28, when used by direct diffusion, were absorbed by the intact rabbit skin and were capable of blocking the vasoconstriction produced by intravenously administered epinephrine. By this route SY-28 was approximately five times as potent as Dibenamine. When the adrenergic drugs were administered by ion transfer, the penetration of both drugs into the skin was significantly facilitated. Both blocking compounds were fixed locally in the skin, but the contiguous untreated areas were still capable of responding to epinephrine. SY-28 when given intravenously was approximately eight times as potent as Dibenamine. The "epinephrine reversal" phenomenon was noted for the first time in the skin of the rabbit and suggests the presence of vasodilator fibers.

MINTZ

Raab, W.: Propyl-thiouracil for Angina Pectoris. Acta med. Scandinav. **135:** 364 (Oct.), 1949.

Nine patients were treated with propyl-thiouracil for five to sixteen months, with daily doses ranging from 100 to 300 mg. One patient, who averaged thirty attacks of angina per month, responded with a complete disappearance of symptoms after nine months of therapy. In 4 other cases there was a definite reduction in the number and severity of the episodes. The improvement was moderate in one case, and slight in another. In 2 cases there was no response whatsoever. In one severe case, the combined treatment of x-ray irradiation of the adrenals and thiouracil was followed by disappearance of the attacks, which have not recurred in thirty-two months.

There were no instances of toxic side effects or of myxedema. However, during the course of therapy there was one nonfatal coronary occlusion, and three fatal ones. There were two other deaths from coronary occlusions which occurred three weeks and six months, respectively, after discontinuing the propyl-thiouracil.

Because atherosclerotic lesions have been produced in dogs by the combined administration of cholesterol and thiouracil, and because of the possible significance of hypercholesteremia in the origin of human coronary sclerosis, the author considers it advisable to maintain cholesterol intake at a mini-

mum when treating a patient for angina with propylthiouracil.

Margolies

DelPozo, E. C., and Pardo, E. G.: Ischemic Striated Muscle as an Indicator of the Activity of a Cardiac Glycoside. J. Pharmacol. & Exper. Therap. **97:** 144 (Oct.), 1949.

Cardiac glycosides have little effect on normal myocardium until toxic quantities have been administered; however, their effects on the "hypodynamic" heart of a failing myocardium is marked. Cardiac glycosides have little action on contractile tissues other than the heart. Skeletal muscle can be subjected to large quantities of glycosides with little effect even though it can be shown that the glycoside is being taken up by the tissue. Theorizing that the failing myocardium is probably anoxic to some extent, the authors administered K-strophanthoside to an anoxic skeletal muscle to see if in this special circumstance the effects of the glycoside in skeletal and heart muscle would be comparable.

Anoxia was produced in the cat's hind limb by temporary occlusion of the aorta. K-strophanthoside was administered intravenously in amounts up to 80 per cent of the minimal lethal dose. The glycoside appeared to have a very marked effect on the strength of contraction, duration of contraction, and degree of relaxation after contraction. It appeared to increase the strength of contraction, shorten the duration and increase relaxation. The effects were only noted after sufficient anoxia had been produced to markedly affect the limb's response to stimulation.

Godfrey

Bohr, D. R., McIvor, B. C., and Rinehart, J. F.: The Effects of Various Flavone Glucosides on the Rate of Passage of Evans Blue through the Damaged Capillary Wall. J. Pharmacol. & Exper. Therap. **97:** 243 (Oct.), 1949.

The ability of rutin and other flavones to decrease capillary permeability has commonly been measured by the skin colorization time after injection of Evans blue into the experimental animal. The authors attack the validity of this test as an indicator of capillary permeability. They found that increase in the skin colorization time could be roughly correlated with the ability of the individual flavone to depress blood pressure, thereby decreasing peripheral capillary blood flow. Furthermore, a very marked decrease in the colorization time could be produced by continuous administration of nitrites (with subsequent marked hypotension). Hespiridin methyl chalcone produced a greater and more substained fall in blood pressure than did either rutin or sodium hesperidin chalcone, and likewise was more effective in producing a delay in skin colorization time.

Godfrey

Glazebrook, A. J.: Clinical Trials of Succinates and of Heparin in Rheumatic Fever. Brit. M. J. **4631:** 789 (Oct. 8), 1949.

Glazebrook and Cookson (1947) have pointed out that substances and conditions benefiting acute rheumatic fever, rheumatoid arthritis, and anaphylactic states have a common action in that they are all anticoagulants. These substances and states are salicylates in rheumatic fever, deep jaundice in rheumatoid arthritis, and heparin in anaphylactic states. On the basis of this theory, the author reports his experiences in the treatment of acute rheumatic fever with: (a) calcium monobenzyl succinate, (50 gr. daily) and (b) calcium double salt of benzoic acid and succinic acid benzyl ester, (50 gr. daily). He also reports his experiences in the treatment of acute rheumatic fever with heparin (1000 T.U. intravenously three times daily) and salicylates (200 gr.) daily in four-hourly doses. A control group was given salicylates, without heparin. All three groups were also given 200 mg. of ascorbic acid daily. None of these methods represented any improvement over conventional salicylate therapy.

Bellet

PHYSICAL SIGNS

Von Reis, G.: Clinical Aspects of Endocardial Myxoma Situated in the Left Atrium. Acta med. Scandinav. **133:** 213 (Apr.), 1949.

The authors summarize the clinical findings in 30 cases of endocardial myxoma situated in the left atrium. These tumors were of such a size that they touched the mitral orifice or ended just above this structure; in all probability they gave rise to the patients' symptoms and led to the fatal termination.

In 8 cases there was heard a systolic murmur, less often a presystolic, and only occasionally a diastolic murmur. In 6 cases three sounds were heard, and in 6 cases an accentuated second pulmonic sound was present. Arrhythmias and electrocardiographic abnormalities of various types were present. In 4 cases, embolic phenomena were present. Initially the patients were but slightly inconvenienced by their symptoms, but as soon as signs of cardiac incompetence appeared, the condition was apt to prove fatal within a short period. Attacks of the Adams-Stokes type seemed to be an invariable feature, without a demonstrable transition into complete heart block. In all probability these attacks occurred when the polypus attained such a size that it temporarily obstructed the mitral orifice. When the patient's position is changed, the polypus may slide back from the orifice, the circulation being re-established and the cerebral anemia alleviated.

Bellet

Alimurung, M. M., Rappaport, M. B. and Sprague, H. B.: Variations in the First Apical Sound Simu-

lating the So-called "Presystolic Murmur of Mitral Stenosis." New England J. Med., **241:** 631 (Oct. 27), 1949.

In 8 patients who on clinical examination presented a presystolic apical murmur, phonocardiography failed to corroborate this auscultatory interpretation. This auditory illusion was due to several forms of variation of the first heart sound, in all of which the whole sound complex assumed a crescendo configuration. These variations consisted in prolongation of the sound, with its later elements of unusual intensity, splitting of the sound in such a fashion that the second element was more intense than the first, and prolongation of the sound in association with an auricular gallop coming very close to the first sound. In all these variations, however, the first sound always started after the electrocardiographic Q wave.

Three cases definitely had valvular disease. Two had rheumatic heart disease with predominant aortic regurgitation and mitral regurgitation; the third was a case of syphilitic aortitis with aortic insufficiency. In the 2 rheumatic cases the association of the aortic diastolic murmur heard at the apex with what was believed to be a presystolic crescendo element led to the additional diagnosis of mitral stenosis which was incorrect. A second group comprised 3 patients with congenital cardiovascular anomalies who were all thought to have associated rheumatic mitral stenosis because of the presence of an apical diastolic murmur with the so-called presystolic crescendo quality. A third group of two patients were considered to have normal hearts.

BELLET

Scherf, D., and Brooks, A. M.: The Murmurs of Cardiac Aneurysm. Am. J. M. Sc. **218:** 389 (Oct.), 1949.

In 3 cases of cardiac aneurysm due to myocardial infarction, a diastolic murmur was registered over the aneurysm with the stethogram. This murmur was high-pitched, gushing and soft. It resembled the murmur heard in aortic regurgitation, but it was present throughout diastole and its intensity increased in presystole. It is believed that passage of blood into the orifice of the aneurysm, which often is narrower than the largest diameter of the sac, causes the murmur. It is difficult to understand, however, why the murmur is louder at the end of diastole.

DURANT

Luisada, A. A., and Alimurung, N. M.: The Systolic Gallop Rhythm. Acta Cardiol. **4:** 309 (Fasc. III), 1949.

Twenty-four cases of systolic gallop rhythm were studied from clinical and phonocardiographic points of view. Age, sex, frequency in relationship to other types of gallop, and symptoms of the patients are reported by the authors.

The systolic gallop may be classified into two types, the basal and the apical or midprecordial. The basal type is early systolic and associated with functional disturbances or anatomic changes of the large arterial vessels. The apical type is midsystolic or late systolic, and, at least in a certain number of cases, is caused by traction of adhesions. The graphic characteristics of these two types of systolic gallops are given. These aid in avoiding misinterpretation of the auscultated snap, an error which occurred in one-third of the cases in the present series. The association of the systolic apical gallop with palpitation, extrasystoles, and brief, stabbing precordial pain is pointed out by the authors and the significance of these symptoms is discussed.

LUISADA

PHYSIOLOGY

Heim de Balsac, R.: The Normal Movement of the Left Ventricle. Rev. argent. de cardiol. **16:** 207 (July–Aug.), 1949.

The normal tracings of the left ventricular movement were studied by means of roentgenkymography. In the anteroposterior position, 96 per cent of the normal subjects show, at the level of the left ventricle (left border of the heart), characteristic large displacements with rectilineal systolic retraction. Either curved (common type) or almost rectilineal (rare type) diastolic expansion may be observed, and secondary waves may be superimposed on this main pattern. Forceful inspiration may greatly diminish the amplitude of these pulsations both in the anteroposterior and right anterior oblique positions, but it causes little change in the left anterior oblique and transverse positions. This factor should be taken into account in order to avoid erroneous interpretations. Findings similar to those of the anteroposterior position are obtained in the oblique positions. The pulsations appear weaker when the left anterior region of the ventricle is examined (right anterior oblique) and larger when the postero-inferior region is visualized (left anterior oblique and left transverse positions).

LUISADA

Hamilton, H. F. H.: The Cardiac Output in Normal Pregnancy. As Determined by the Cournand Right Heart Catheterization Technique. J. Obst. & Gynec. Brit. Emp. **56:** 548 (Aug.), 1949.

Using the heart catheterization technic of Cournand, the author determined the cardiac output in 24 nonpregnant women and in 68 normal pregnant women. In the selection of the patients for this study, all were excluded who did not appear to have a normal cardiovascular system. Patients with a blood pressure over 140/80 and those with a hemoglobin below 60 per cent were excluded. All patients in the study were clinically and radiologically free from pulmonary disease.

In the nonpregnant women the mean cardiac output was found to be 4.51 ± 0.38 liters per minute. In pregnant women, cardiac output was found to rise during the tenth to thirteenth week of pregnancy, reaching an average maximum of approximately 5.73 liters per minute during the twenty-sixth to the twenty-ninth week, an increase of 27 per cent above the nonpregnant level. There was a return to almost normal levels during the thirtieth-eighth and fortieth week. The return of cardiac output to normal levels before the onset of labor is of clinical interest since the work of the heart has thus decreased during the last weeks of pregnancy and it is under optimal conditions by term, with obvious benefit to the patient with a diseased heart.

SCHWARTZ

Palmer, A. J., and Walker, A. H. C.: The Maternal Circulation in Normal Pregnancy. J. Obst. & Gynec. Brit. Emp. **56**: 537 (Aug.), 1949.

The authors investigated the changes in the maternal circulation during pregnancy and the puerperium in 88 normal women by means of cardiac catheterization. Similar studies were carried out on 8 nonpregnant women who served as controls. The mean cardiac output of all the pregnant subjects was 5.8 liters per minute, and 4.6 liters per minute for the nonpregnant control series. The means for the successive months of pregnancy, beginning with the third month, showed no real deviation from the grand mean of 5.8 liters per minute except at the seventh month. A fall in mean cardiac output and a rise in mean arteriovenous oxygen difference was noted temporarily in the seventh month, findings which the authors suggest were probably due to the effect of posture.

It is concluded that both laboratory and clinical studies show that the response of the maternal circulation to the presence of a fetus begins very early in pregnancy and persists until the eighth month. There is a return towards normal in the last month or two. During the first eight months the placenta resembles an arterio-venous shunt. In the last two months, however, the resemblance is definitely less marked. This may be due to a rapid increase in fetal growth rate at that time, with a concomitant increase in oxygen utilization per cc. of blood by the fetus. This concept of the placenta acting first as an arterio-venous shunt and later more like a blood depot as regards its effects on the maternal circulation is a possible explanation of the mechanical factors involved. The endocrine changes of pregnancy must play a considerable part in initiating these modifications.

SCHWARTZ

Davis, J. O., and Shock, N. W.: The Effect of Body Position and Reference Level on the Determination of Venous and Right Auricular Pressure. Am. J. M. Sc. **218**: 281 (Sept.), 1949.

The experiments performed in this investigation demonstrate an increase in antecubital venous pressure with a change in body position from a supine to an erect posture. The phlebostatic axis of Winsor and Burch was used as a reference level. Equivalent results were obtained using either the phlebomanometer of Burch and Sodeman or the saline manometer of Moritz and von Tabora.

No conclusion can be drawn from the available data as to the mechanism for the observed increase. It is suggested that the high venous pressure in sitting positions is not the result of the pressure of surrounding structures on the proximal veins. Failure of the venous pressure to rise with the assumption of the sitting position in some patients precludes the establishment of normal standards in various sitting positions. The right auricular pressure decreased in each of 2 subjects with a change from the supine to a 45 degree sitting position. It is suggested that this fall in intracardiac pressure is the result of a shift in blood from superior to inferior parts of the body by gravity.

DURANT

Fetcher, E. S., Hall, J. F., Jr., and Shaub, H. G.: The Skin Temperature of an Extremity as a Measure of its Blood Flow. Science **110**: 422 (Oct. 21), 1949.

In an investigation of the value of skin temperature as a measure of blood flow, it was found that at room temperature the surface temperature of a finger bore no relation to changes in blood flow. At 25 C., no significant difference was noted. However, at a room temperature of 7 C., there was a close parallel between the two measurements.

The authors conclude, that when skin temperatures are used to measure blood flow, the area under investigation must lose heat at a rate of over 240 Kg.-cal./hr/m^2.

WAIFE

Hesse, H., and Minkus, R.: An Intrathoracic Study of the Movements of the Heart in a Self Experiment. Ztschr. f. Kreislaufforsch. **38**: 613, (Oct.), 1949.

In order to study the systolic movements of the ventricles, anteroposterior and lateral x-ray chest films were taken on one of the authors with a pair of needles introduced into his heart through the third and fourth intercostal space in the left parasternal line. The analysis of the shadows which were produced by the systolic movements of the needles revealed a first motion in median direction followed by a second sagittal movement in a cephalad direction. A slight delay of the latter movement (shown by the needle in the higher position) indicated that the ventricular contraction wave progresses from the apex towards the basis. These movements contribute to the configuration of the average ventricular kymogram.

PICK

Heymann, W., and Salehar, M.: Blood Pressure in the Rat. Proc. Soc. Exper. Biol. & Med. **72**: 191 (Oct.), 1949.

In unanesthetized, untreated rats kept on Friskies and water, the blood pressure was measured with the foot method. Readings obtained about one minute apart in the same animal rarely differed more than plus or minus 3 mm Hg. The systolic blood pressure increased with age in the growing rat. Within the first two months, up to a weight of 150 grams, the pressure increased rapidly. A slower, but progressive rise in pressure was found in rats weighing 200 to 350 grams.

MINTZ

Stotz, E.: Solubilization and Separation of Components of the Heart Muscle Oxidase System. Science **110**: 442 (Oct. 28), 1949.

Heart muscle contains relatively large amounts of cytochrome oxidase, cytochromes A, B and C and succinic dehydrogenase. In the past only cytochrome C, because of its stability towards acid, has been satisfactorily characterized.

From heart muscle subjected to digestion by several types of enzymes, relatively purified cytochrome oxidase was prepared. Furthermore, preparations of soluble cytochrome A with very low cytochrome oxidase activity were made. In addition, a concentrated soluble succinic dehydrogenase was obtained. Further purification and separation of these components of oxidative metabolism is likely to be obtained with the soluble forms.

WAIFE

ROENTGENOLOGY

Grishman, A., Poppel, M. H., Simpson, R. S., and Sussman, M. L.: The Roentgenographic and Angiocardiographic Aspect of (1) Aberrant Insertion of Pulmonary Veins Associated with Interatrial Septal Defect and (2) Congenital Arteriovenous Aneurysm of the Lung. Am. J. Roentgenol. **62**: 500 (Oct.), 1949.

The authors describe three instances of the insertion of right pulmonary veins into the inferior vena cava and describe the appearance in conventional roentgenography. Following angiocardiography, each of these was demonstrated to be associated with an interatrial septal defect. On cardiac catheterization there was a higher oxygen concentration in the inferior than in the superior vena cava. The association of aberrant insertion of pulmonary veins with interatrial septal defect was compatible with long life. The septal defect usually was high above the fossa ovalis.

The authors also describe three instances of pulmonary arteriovenous aneurysm. The diagnosis was confirmed by angiocardiography. They stress the frequent occurrence of aberrant and accessory pulmonary arteries and veins.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Beck, C. S.: Revascularization of the Heart. Surgery **26**: 82 (July), 1949.

In an attempt to increase the total blood supply to the heart, the author performed various types of anastomoses in dogs. In one the purpose was to deliver arterial blood to the coronary sinus, either by anastomosis between the common carotid artery and the coronary sinus or by a free graft of vein between aorta and coronary sinus. It was found that the amount of blood delivered to the coronary sinus by the common carotid could be tolerated, while with the jugular vein graft off the aorta, the amount of blood reaching the heart was so great that almost invariably the animal went into congestive heart failure and died. However, when the jugular vein was constricted so that its lumen was approximately the size of the carotid artery, this did not occur. The possibility of the application of such procedures to patients with coronary artery disease is discussed.

ABRAMSON

Freeman, N. E., Leeds, F. H., and Gardner, R. E.: A Technique for Division and Suture of the Patent Ductus Arteriosus in the Older Age Group. Surgery **26**: 103 (July), 1949.

In an attempt to maintain the circulation through the aorta while dividing a patent ductus arteriosus, the authors utilized a modification of the Potts-Smith clamp. First a pericardiotomy was performed so that the left pulmonary artery could be occluded with digital pressure, and then the clamp was placed around the aorta so as to isolate the aortic region of the ductus. A ligature on the pulmonary end of the ligamentum arteriosum was tied and the latter was divided, followed by excision of the ligamentum with a small portion of the aortic wall. The opening in the aorta was closed and the clamp was removed.

ABRAMSON

Charlier, R.: A Case of Tetralogy of Fallot. Contraindication for Operation based on Pathophysiologic Studies. Acta. Clin. Belg. **4**: 280 (July–Aug.), 1949.

In a case of tetralogy of Fallot information obtained by catheterization of the right heart, determination of the oxygen saturation in the periphery, and Bing's exercise test revealed a right to left shunt of only minor degree and moderate reduction in the blood flow through the pulmonary artery. Therefore, an operation did not seem indicated. The author emphasizes the necessity of such studies in order to avoid unnecessary operations.

PICK

Miller, B. J., Gibbon, J. H., Jr., and Allbritten, F. F., Jr.: Blood Volume and Extracellular Fluid Changes During Thoracic Operations J. Thoracic Surg. **18**: 605 (Oct.), 1949.

The authors discuss various observations made on measurements of the amount of blood lost during operations and its replacement. The blood loss computed by the dye method is believed to be more indicative of the actual blood loss than when computed by the sponge weight method, since small quantities of blood may escape detection by the latter method.

The fluid available for the dilution of sodium thiocyanate, hereafter referred to as the extracellular fluid, was determined both preoperatively and postoperatively as ferric thiocyanate. In a series of 57 patients, blood volume was measured by the dye method before, and immediately following, a major thoracic operation. Blood volume was calculated from the plasma volume and the hematocrit. The extracellular fluid volume was measured with sodium thiocyanate both preoperatively and postoperatively in 33 patients in this series. Blood loss during operation was measured by the sponge weight method in 27 instances. The blood lost during operation was more accurately replaced by transfusion when the sponge weight method was used. At present this is the only method which gives a continuous record of the blood lost during the course of an operation, and hence, permits simultaneous accurate replacement by blood transfusions. Significant losses of extracellular fluid usually occurred during long operations.

BECK

Lam, C. R.: The Choice of the Side for Approach in Operations for Pulmonary Stenosis. J. Thoracic Surg. **18**: 661 (Oct.), 1949.

The author reports the results of fifty operations for pulmonary stenosis or atresia. Thirty-one Blalock and fifteen Potts operations were carried out. In 4 cases, no shunt was completed. Reports of 2 of these cases are presented, as well as reports of 2 other cases which presented marked technical difficulty. The anatomic peculiarities and technical difficulties present in a right subclavian-pulmonary anastomosis are discussed and compared with the advantages of anastomosis on the left side. If the danger of compromising the free flow of blood through the shunt is considerable, then this one disadvantage in using the left approach outweighs all the advantages. However, some evidence is presented which makes this danger more theoretic than real. In order to choose freely between the Blalock or Potts procedures after the chest is opened, one should enter the chest anteriorly. As a result of the experience in these fifty operations, the following simple rule was adopted for choosing the side for operative approach in the individual case: The incision is made on the side of the apex of the heart, regardless of the position of the aortic arch or the age of the patient.

BECK

Ruprecht, A. L., and Adelman, A.: Unsuspected Trauma to the Heart During Intrathoracic Surgery. New England J. Med. **241**: 637 (Oct. 27), 1949.

The authors present 2 cases of inadvertent damage to the heart during surgical procedures on other thoracic viscera. A total gastrectomy was performed through a thoracoabdominal incision on a 63 year old man. During the retraction of the diaphragm, there was an abrupt onset of tachycardia, the heart rate rising from 80 to 120 per minute. Except for this transient disturbance, the patient's operative course was uneventful. Within four hours he developed signs of circulatory collapse. Shock supervened and death occurred fifty-three hours after operation. At autopsy the pericardial sac was distended by several hundred cubic centimeters of partially clotted blood. The site of hemorrhage was an injured coronary vein on the anterior aspect of the left ventricle. The heart was probably injured during anastomosis of the esophagus and jejunum.

A left pneumonectomy was performed on a 44 year old man. About five minutes after adjusting the intrapleural pressure, respirations and heart beat suddenly ceased. At autopsy the right auricle and ventricle were found to be dilated and engorged with blood. Over the anterolateral aspect of the left ventricle, the subepicardial fat was hemorrhagic. The underlying muscle was discolored, purplish red and was softer than elsewhere, this lesion involving from the outer fifth to half of the ventricular wall and extending from the auriculoventricular groove to within 4 cm. of the cardiac apex. Although myocardial injury was suggested by the tachycardia, this sign of muscle damage was not appreciated. Asystole and ventricular fibrillation have been observed after experimental contusion of the heart, and it is likely that one of these disturbances was responsible for the patient's death.

The heart may not be bruised frequently during operations in the thorax, but an important factor in the recognition of cardiac insult is an awareness of the possibility. A diagnosis of cardiac injury should be suspected in any patient who maintains an unexplained tachycardia after an intrathoracic operation or in whom an arrhythmia or pericardial friction rub develops. If electrocardiograms are taken before and after operation better evidence of cardiac injury may be available.

BELLET

Dodrill, F. D.: A Method for Exposure of the Cardiac Septa. An Experimental Study. J. Thoracic Surg., **18**: 652 (Oct.), 1949.

An instrument is described by which the right side of the heart, either the right atrium or the right ventricle, may be opened and the septum exposed for varying lengths of time. The length of time which the heart will withstand the clamp in place varies considerably. The instrument makes it possible to expose an area of the septum 2 to 2.5 cm. in diam-

eter. Various technical procedures can be carried out on the septa under direct vision. The incision in the right side of the heart is then closed. About 50 such operations have been performed on dogs. Although the mortality rate at first was approximately 50 per cent, it is now possible to expose either the interatrial or interventricular septum with only an occasional death of the animal. This is particularly true in dealing with the interatrial septum since the instrument may be released at any time.

BECK

Gius, J. A.: Some Observations on Vascular Adjustments following Interruption of Major Venous Channels. West. J. Surg. **57**: 453 (Oct.), 1949.

The author calls attention to the fact that the venous system has a great capacity to adjust to sudden occlusion of its major trunks. Whether or not the compensatory mechanisms will be adequate is dependent upon such factors as the calibre and level of the vein occluded, the efficiency of the anastomoses and collateral vessels, the degree of existing vasospasm, the previous presence or absence of pathologic changes in the distal veins, the demands placed on the venous circulation locally by physiologic activity, and the effect of hydrostatic forces. In the event that edema does occur, uniform compression and elevation of the extremity can be utilized to aid tissue fluid absorption. Even in the absence of antecedent disease of the vein wall, interruption of a major venous channel, such as the inferior vena cava, may precipitate acute thrombosis of the distal circulation as a result of the sudden stagnation. In order to prevent this, it is necessary to utilize anticoagulant therapy, elevation of the extremity and means to counteract vasospasm.

ABRAMSON

Burdette, W. J.: Removal of the Auricular Appendage in the Dog. Surg., Gynec. & Obst. **89**: 623 (Nov.), 1949.

Both auricular appendages were removed in 16 dogs in an attempt to elucidate the practicability of such a procedure in the prevention of emboli arising in this location in man. Although arrhythmia invariably occurred when the auricular appendage was first grasped and later when the base was being sutured, the changes were only transitory and were no longer present by the time the operation was completed. All of the animals survived the removal of one appendage, while one died shortly after the second operation. When both appendages were removed in one stage the mortality was much greater. No deleterious effects were noted following the operation. As a result, the author suggests that a similar type of procedure might have therapeutic possibilities in man.

ABRAMSON

THROMBOEMBOLIC PHENOMENA

Homans, J.: The Management of Recovery from Venous Thrombosis in the Lower Limbs. Surgery **26**: 8 (July), 1949.

The author attempted to evaluate the procedure utilized during the recovery period from venous thrombosis of the lower extremities. His report is based upon a study of 55 patients with phlebothrombosis in whom conservative measures, vein ligation or anticoagulant therapy had been used during the acute phase of the condition. For the 30 cases treated with interruption of the superficial vein, the postoperative management consisted of rest in a bed elevated 4 inches at the foot for approximately a week, during which all evidence of thrombosis generally disappeared. Under such a regimen the author noted excellent results in 21 patients, slight residual edema in 5, while in 2, previously existing varicose veins recurred and progressed. The remaining 2 cases could not be traced. From the results, it was concluded that superficial vein interruption for thrombosis confined to the leg is not very harmful to the venous return.

In the case of unilateral interruption of the common femoral vein an immediate postoperative thrombotic reaction, marked by swelling and lameness in the calf, was much more common. Later, edema and venous congestion were not infrequently noted. However, a carefully controlled convalescence appeared to be of value in minimizing these complications.

Ten patients were treated by anticoagulant therapy. Of the 3 in whom there was high femoral vein involvement, physiotherapy in the convalescent period produced especially good results.

The author concludes that during convalescence from a deep venous thrombosis, the consistent use of gravity drainage, graded exercises, bandaging and the proper balance between dependency and elevation is of advantage in the establishment of a permanently efficient collateral venous return from the lower limbs. The initial treatment of the condition by anticoagulants with preservation of the common femoral pathway appears to result in fewer complications than are observed after surgical interruption of the common femoral vein. Superficial femoral vein section, although a relatively harmless interruption, offers insecure protection against embolism unless supported by anticoagulant therapy. Since the venous connections between the deep and superficial femoral veins are numberous, ligation of the latter will result in little interference with venous return, provided the common femoral vein is open.

ABRAMSON

BOOK REVIEWS

Arterial Hypertension. *David Ayman, M.D.* New York, Oxford University Press, 1948. 94 pages, 9 charts. $2.50.

This work is reprinted from Oxford Loose-Leaf Medicine. In 86 pages, the etiology, pathology, symptoms, signs, differential diagnosis and treatment of hypertension are surveyed.

Ayman does not believe that experimental renal hypertension has any similarity to essential hypertension, and therefore feels that any consideration of it is beside the point. He stoutly maintains that essential hypertension is an hereditary disease, the mechanism of which is wholly unknown. This viewpoint is one which, for a variety of reasons, is not completely satisfying. It is, however, proper to emphasize that no proof has been offered that the sole cause of essential hypertension is renal.

Especially to be commended is the stress put on the need for adequate control periods in evaluation of experimental treatment. The author was largely responsible for the interesting study of blood pressure taken by patients themselves in the home, demonstrating that the average blood pressure level under this circumstance is usually well below the level found in the physician's office. He is also identified with a remarkable demonstration of the "effectiveness" of placebos. A third facet of especial interest is identification of the symptomology of arterial hypertension with that of psychoneurosis. This accounts for the fact that symptoms are improved or cured by such a variety of "treatments," several hundred of which have been suggested or practiced in the past fifty years.

This book is welcomed as a substantial addition to the literature on hypertension for the more than usually discerning and industrious physician, and is heartily recommended.

Irvine H. Page
Arthur C. Corcoran

Corazon Pulmonar e Insufiencia Coronaria. *Juan Govea, M.D.* Havana, Cuba, M. V. Fresneda, 1948. 178 pages, 70 figures.

In spite of its title, which would lead one to think of *cor pulmonale* as being its principal subject, this monograph is almost entirely devoted to the study of the coronary arteries and the consequences of their occlusion. A major part of the book is devoted to fundamentals. Current notions on the anatomy and physiology of the coronary circulation are reviewed; the theory and practice of precordial electrocardiography are analyzed in some detail, especially with reference to their role in analyzing cardiac infarction; a chapter is devoted to radiology of the heart. One chapter is devoted to "Ayerza's disease" and the rest of the book deals with personal concepts on different types of coronary insufficiency.

The topics are dealt with in an incomplete manner, most of the interpretations being too personal. The language is often vague. Illustrations are poor.

Oscar Orias

Las Arritmias en Clinica. *Antonio Battro, M.D.* Buenos Aires, El Ateneo, 1948. 511 pages, 299 figures.

This well organized and well written book appeared only a few months before the regrettable death of the author, an outstanding Argentine cardiologist. The first part of the book is devoted to the anatomy and physiology of the heart and to the graphic methods of recording its activity. Among the latter, electrocardiography has received particular attention. This pertinent chapter includes the discussion of the standard limb leads, precordial leads, monopolar limb leads, and endocardiac potentials in man, the last mentioned being a field in which the author himself was a pioneer. The rest of the book (about two-thirds) is devoted to a systematic presentation of the different arrhythmias, including their etiologic factors, diagnosis, prognosis and treatment. Controversial matters are fairly presented with due consideration of all viewpoints.

The book is well printed and the figures—the great majority being original records—portray two or more manifestations of the cardiac activity clearly and adequately. It can be highly commended as useful to all students in this field.

Oscar Orias

Arterial Hypertension. A Follow-up Study of One Thousand Hypertonics. *Poul Bechgaard.* Copenhagen, Denmark, Arnold Busck, Nyt Nordisk Forlag, 1946. 358 pages, 23 figures.

This book gives a rather complete review of hypertension and renal disease. Etiology is discussed in terms of obesity, heredity, renal diseases, and other factors. There is no attempt to review the literature of experimental medicine as regards this subject. One thousand patients have been carefully investigated. The morbidity and mortality in these cases are examined and carefully correlated with other existing conditions, such as syphilis, renal disease, retinopathy, and diabetes mellitus. These

is no discussion of therapeutic methods or their influence upon the problem. This book should be most useful to those interested in the natural unaltered course of hypertension regardless of cause. It should provide a background or measuring stick in evaluating present day therapeutic efforts.

JOSEPH A. WAGNER

Clinical Auscultation of the Heart. *Samuel A. Levine, M.D., and W. Proctor Harvey, M.D.* Philadelphia, W. B. Saunders Company, 1949. 327 pages, 286 figures.

This work is an excellent correlation of the clinical recognition of heart sounds and murmurs and phonocardiograms. As the title implies, the book is essentially clinical. There is little of physiologic interpretation. There is no discussion of the physical characteristics of the recording apparatus. The book is clearly written and the illustrations are good and are well chosen. This book will aid the student and physician in understanding the sound vibrations that are heard. The monograph is recommended for clinical use.

HAROLD FEIL

The 1949 Year Book of Medicine. Part IV. The Heart and Blood Vessels. *Tinsley R. Harrison, M.D., Ed.* Chicago, The Year Book Publishers, 1949. 831 pages, 139 figures. $5.00

The caliber of the 1949 Year Book of Medicine is every bit as good as that of past editions. The extracted articles in the chapter on the heart and blood vessels have been well selected from the literature of the preceding year by the Editor. His short preface to each subdivision of the chapter provides the reader with a useful introduction to the subject. As in the past, this volume is excellent for those who have not the time or the facilities to keep abreast of the tremendous number of publications which appear in medical journals.

THOMAS W. CLARK

Unipolar Lead Electrocardiography, ed. 2. *Emanuel Goldberger, M.D.* Philadelphia, Lea & Febiger, 1949. 392 pages, 221 illustrations. $7.50.

This book is an enlarged and revised version of the author's previous work, but contains, in addition, a section relating to the use of the electrocardiogram in the cardiac arrhythmias.

After a brief but fairly adequate discussion of apparatus, basic electrical concepts and methods for taking unipolar electrocardiograms, in the first three chapters, five basic patterns of the ventricular complex that may be expected in unipolar electrocardiograms taken on subjects with normal hearts are described. With these patterns in mind, the author builds a rather elaborate group of criteria based on the form of the ventricular complex in precordial and unipolar extremity leads by means of which rotation of the normal heart about the three possible axes can be identified. Although there may be much truth in these concepts, their validity can also be questioned. Many cardiologists, including the reviewer, feel that caution must be observed in the interpretation of the ventricular complex in unipolar precordial or extremity leads when the voltage in either is small or when the former are taken from points located at a considerable distance from the heart. Tracings taken from points over the precordium close to the heart in all probability reflect the potential variations at the surface of the underlying ventricle, but this may not be true in tracings obtained from sites on the chest remote from the heart or in the unipolar extremity leads.

The discussions of right and left ventricular hypertrophy and bundle branch block are, in general, satisfactory, and those of myocardial infarction, effects of changes in electrolytes and the arrhythmias are good. An extensive list of references is provided.

The material in the book is not well organized, and in many places one gets the impression that it was written hurriedly and without the care that is necessary to convey exact meanings to the reader. The author gives the impression that he is not very critical of his own efforts, and some of the electrocardiograms presented are poor or completely inaccurate examples of the thing they are supposed to illustrate. For example, Figure 54 is labelled "Additional Electrocardiograms of Normal Vertical Hearts," but the tracings presented under "b" in this figure do not illustrate this situation, and the tracings labelled "c" and "d" may be abnormal because of QRS deflections of large voltage.

Throughout the book, the author gives the impression that unipolar extremity leads have much greater advantages over the conventional standard leads than is actually the case. One must remember that many of the criteria for normality (or abnormality) of electrocardiograms have been gained by study of the standard leads and correlations between them and patients gained over a long period of time. Unipolar extremity leads do not, in the opinion of the reviewer, often add information not also present in the standard leads. The former are occasionally helpful in the interpretation of changes occurring in the latter, and the unipolar extremity tracings serve to relate findings in standard to those encountered in precordial curves.

The reviewer wishes, however, to commend the author on most of the opinions expressed in Appendix I under the heading "Some Electrocardiographic Observations." Items 1, 2 and 23 are particularly important and indicate an appreciation of the place the electrocardiogram should occupy in the field of cardiac diagnosis.

F. D. JOHNSTON

Arterial Hypertension. Its Diagnosis and Treatment, ed. 2. *Irvine H. Page and Arthur C. Cor-*

coran. Chicago, The Yearbook Publishers, 1949. 400 pages, 19 figures. $5.75.

There was no need for the complete rewriting of such a good book, and this has not been done; but portions on which new knowledge has appeared during the past five years since the publication of the first edition have been entirely rewritten or corrected. A valuable new chapter has been inserted on the nature, diagnosis and treatment of hypertension due to known or attributable causes. The section on the renal aspect of hypertension has been modified and now includes the discussion of hypertension on the basis of unilateral renal disease and its treatment by nephrectomy. Dieto-therapy is treated independently, instead of being distributed throughout the book. The subject of low sodium and so-called rice diet treatment is handled with fairness, and detailed instructions as well as warnings about the use of these methods are included. The value of vitamin E and of rutin are discussed. Recent experiences of the authors with the treatment of malignant hypertension by means of pyrogenic substances are given in some detail as a separate chapter. There is a valuable appendix which gives methods and procedures used in the diagnosis of hypertension as well as detailed information about the low sodium diet. An excellent book has been brought up-to-date.

HARRY GOLDBLATT, M.D.

Physiology in Diseases of the Heart and Lungs. *Mark D. Altschule, M.D.* Cambridge, Mass., Harvard University Press, 1949. 363 pages. $5.00.

This valuable book differs widely from anything else in the field. It is essentially a most elaborate review of the literature, very thoroughly documented. Indeed the references, many appearing several times because they are cited in more than one chapter, take up about one-third of the book. For any one wishing to investigate the literature in this field this book will be the ideal starting place and it will undoubtedly be found on the shelf of every active investigator interested in the physiology of cardiovascular disease.

The book suffers from the faults inherent in most comprehensive review articles. The style is extraordinarily compressed, and, repeatedly cut up by brackets containing authors names; the book is very hard to read. Those looking for new and simple conceptions to unify and make understandable the welter of data will be disappointed, for the author has no new contribution to make. Indeed, he is still engaged in defending the idea that an abnormal relation between cardiac output and metabolism is a chief factor in the genesis of congestive failure; whereas the reviewer believes that this idea, which formed the theoretic basis for the operation of total thyroidectomy, has been tested and found wanting by the failure of that operation to help most patients, with its consequent abandonment by most clinics.

The author also has a tendency to dismiss results which diverge from his expectations by a wave of the hand, whereas one inclined to a contrary view would have the right to ask whether the evidence for reliability, so scanty in many methods applicable to the sick, was not every bit as good as in those methods yielding results in which the author has full confidence.

But certainly no one could cover this field in a way which would please everybody, and this is a sign that it is in a healthy state and rapidly growing. Indeed the book gives convincing evidence of the energy and vigor of the physiologic school of thought now so important in clinical medicine in the United States. For its viewpoint, concerned with cardiac output, cardiac work, respiratory dynamics, metabolic changes and the like, will be of far greater service in meeting the needs of our patients than the description of diseased conditions, of physical signs, and the concern for pathologic diagnosis which has been the burden of so many books on cardiac and pulmonary disease in the past.

ISAAC STARR

Electrocardiographic Technique. A Manual for Physicians, Nurses and Technicians. *Kurt Schnitzer, R.T., M.D.* New York, Grune and Stratton, 1949. 96 pages, 46 figures. $3.50.

This manual represents a brief introduction into the technical problems of electrocardiography, illustrated both diagrammatically and with photographs. One-third of the text is devoted to the manner of lead selection, the remainder to a discussion of the principles of an electrocardiograph, the preparation of the patient and to some of the problems of diagnosis and cure of external interferences. Six pages are devoted to general remarks on special procedures (esophageal and endocardial leads, anoxemia test and fetal electrocardiography). The book is elementary and, not intended as a technical guide to the many day by day problems of a cardiographic laboratory, still provides a sound basis for the technician.

HANS H. HECHT

Rhumatisme Articulaire Aigu (Maladie de Bouillaud). *R. Lutembacher, M.D.* Paris, France, Masson & Cie, 1947. 438 pages.

This monograph is a systematic treatise on rheumatic fever. The history of the development of our knowledge of this disease and its clinical and pathologic manifestations are treated with thoroughness characteristic of the best French clinicians. The pathologic involvement of the tissues of the body is illustrated by many photographs, and pulmonary

localization of the rheumatic infection, especially in children, receives much prominence. Chapters are devoted to pathologic lesions in the liver, pancreas, kidneys and nervous system. The author's insistence that myocarditis is crucial in the problem of rheumatic fever is well supported by case histories and will be endorsed warmly by American clinicians and investigators.

Much discussion is devoted to the author's methods of treatment which he has followed since 1921. The emphasis is on the use of salicylates, Antipyrine and Pyramidon, given by the intravenous route. His practice of administering salicylates over periods of as long as two years is not followed by English and American physicians so far as the reviewer knows, nor is he aware that other clinicians in America have employed these drugs in the intensity or for the duration that Lutembacher advocates; it may be expected, however, that the enthusiasm displayed by the author for his systems of treatment will be received with much skepticism by physicians in English-speaking countries.

The writer reviews the probable factors responsible for rheumatic fever. He cites evidence that the disease has a partial basis in "the soil" or diathesis favorable to its development, reviews the evidence for the anaphylactic basis for rheumatic fever and recounts the evidence for the role that bacteria play in the production of this disease. He admits that no one of these furnishes a satisfactory explanation of rheumatic fever, but does conclude that rheumatic fever is a specific disease entity.

The reading of this monograph will richly repay the student of rheumatic fever since it emphasizes its protean manifestations and the multiplicity of tissues and organs that are involved in the pathologic processes of the disease.

ARLIE R. BARNES

AMERICAN HEART ASSOCIATION, INC.

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A preliminary schedule of sessions at the 1950 Annual Meeting of the Association at the Fairmont Hotel, San Francisco, includes:

Thursday, June 22:	Scientific Council meeting (10 A.M. to Noon).
	Scientific Session (afternoon); topic—Rheumatic Fever and Infectious Diseases.
Friday, June 23:	Scientific Session (morning); topic—Circulation.
	Scientific Session (afternoon); topic—Cardiology.
Saturday, June 24:	Scientific Session (morning); miscellaneous topics.
	Assembly meeting (afternoon).
Sunday, June 25:	Assembly meeting (morning).
	Luncheon and Board of Directors meeting.

STANDARDS APPROVED FOR CARDIOVASCULAR CLINICS

"Recommended Standards and Minimum Requirements for a Cardiovascular Clinic" is the title of a pamphlet just issued by the Association and available gratis. Prepared by the Committee on Cardiovascular Clinics, the report has been approved by the Board of Directors.

The Recommended Standards and Minimum Requirements are designed to encourage and to aid the establishment of cardiovascular clinics which will provide the best available service to patients, as well as clinical material and research facilities for the professional personnel, to promote better understanding of cardiovascular problems.

Recognizing that many communities are limited in the facilities and services available, the minimum requirements, representing the essentials that must be provided in any community if satisfactory clinic service for cardiovascular patients is to be provided, are printed in bold type throughout the pamphlet. Additional recommended standards are printed in lightface type. Eligibility for approval by the Association and procedures to obtain such approval

are presented. Clinic approval, subject to reexamination and renewal every two years, will be confirmed by a certificate issued by the American Heart Association.

A Standing Committee on Cardiovascular Clinics of the Scientific Council, with representatives from the Council, affiliated heart associations and the Staff Conference of Heart Associations, is being formed and will hold its first meeting at the Annual Scientific Sessions in June. In addition to overseeing standards and certification of cardiovascular clinics, this committee will assemble data on personnel, equipment, policies and management of the clinics so approved.

ADDITIONAL RESEARCH AWARDS ANNOUNCED

The Board of Directors, on recommendation of the Research Committee of the Scientific Council, has approved 46 Grants-in-Aid totalling $219,837. These awards, together with $49,800 allocated from cooperative research funds and $128,497 in previously announced allocations for Established Investigators and Research Fellows, bring to a total of $398,134 the funds voted by the Association over the past year for research in 1950–51. This total allocation represents the complete research allotments out of funds raised in the 1949 Heart Campaign a year ago.

The 46 awards represent 24 new Grants-in-Aid (totalling $116,791), seven Continuing Grants-in-Aid ($29,708), seven Grants-in-Aid in projects previously supported by the American Foundation for High Blood Pressure (now the Council for High Blood Pressure Research of the American Heart Association) ($28,903), three grants for Basic Research ($27,530), and five Grants-in-Aid to Established Investigators and Research Fellows ($16,905). The awards follow:

Continuing Grants-in-Aid

Yale University School of Medicine, New Haven, Conn., for the study of cardiotropic substances in human blood, by *William T. Salter*. Original grant 2 years. ($3,616.20)

The University of Pennsylvania School of Medicine, Philadelphia, Penn., for the study of cardiac output, peripheral resistance, and arterial temperature in man as affected by heat and cold, by *H. C. Bazett*. Original grant 2 years. ($5,880.00)

Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif., for the study of relationship of changes in plasma and tissue sodium to the development of "shock" in myocardial infarction, by *John J. Sampson*. Original grant 3 years. ($3,360.00)

The University of Kansas School of Medicine, Kansas City, Kansas, for studies of the influence of mineral deficient states particularly calcium on the heart and blood vessels, by *Mary C. Colglazier*. Original grant 2 years. ($5,250.00)

Duke Hospital, Durham, N. C., for the study of the nature of hypertension association with coarctation of aorta, by *W. C. Sealy*. Original grant 2 years. ($3,412.50)

The University of Tennessee College of Medicine, Memphis, Tenn., for the development of methods for detection of altered pathways of blood flow through the kidneys of intact dogs under various experimental conditions, by *C. Riley Houck*. Original grant 3 years. ($3,780.00)

Syracuse University College of Medicine, Syracuse, N. Y., for the study of nervous and hormonal control of intrarenal blood flow, by *Otto W. Sartorius*. Original grant 2 years. ($4,410.00)

New Grants-in-Aid

Western Reserve University School of Medicine, Cleveland, Ohio, for the study of the interrelationship between vascular disease, diabetes, and glutathione, by *Arnold Lazarow*. Duration 1 year. ($4,200.00)

Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, Calif., for a study on (a) mechanism of proteinuria, (b) the relation between adrenal cortex activity and experimental renal hypertension, (c) the relation between the adrenal gland and the pressor and proteinuric effects of renin, by *Jessie Marmorston*. Duration 1 year. ($4,200.00)

Columbia University, College of Physicians and Surgeons, New York, N. Y., for the study of the response of the splanchnic circulation to stress in normal and hypertensive subjects, by *Stanley E. Bradley*. Duration 1 year. ($4,200.00)

McGill University, Faculty of Medicine, Montreal, Canada, for the study of desoxycorticosterone acetate induced hypertension, by *Sidney M. Friedman*. Duration 1 year. ($2,863.64)

Long Island College of Medicine, Brooklyn, N. Y., for the study of the structural aspect of tubular activity of the nephrons in the metabolism of protein, by *Jean Oliver*. Duration 1 year. ($2,940.00)

Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif., for the study of the metabolism and excretion of cholesterol, by *Meyer Friedman*. Duration 1 year. ($6,300.00)

Washington University School of Medicine, St. Louis, Mo., for the study of aging and calcification mechanism of the human cardiovascular system, by *Albert I. Lansing*. Duration 1 year. ($4,200.00)

Western Reserve University School of Medicine, Cleveland, Ohio, for the study of myocardial metabolism, by *Victor Lorber*. Duration 3 years. ($10,395.00)

Tulane University of Louisiana School of Medicine, New Orleans, La., for the study of cytochemical and histochemical approaches to renal physiology, with particular reference to electrolyte reabsorption in congestive failure, by *Nathaniel B. Kurnick*. Duration 3 years. ($9,135.00)

Marine Biological Laboratory, Woods Hole, Mass., for the study of the molecular mechanism of muscular contraction, by *Albert Szent-Gyorgyi*. Duration 1 year. ($8,000.00)

Bowman Gray School of Medicine, Winston-Salem, N. C., for the study of the immunophysiology of rheumatic fever, by *Jerry K. Aikawa*. Duration 1 year. ($3,150.00)

Yale University School of Medicine, New Haven, Conn., for the study of (a) vasoconstriction and hypertension, (b) cholesterol and arteriosclerosis, by *John H. Heller*. Duration 1 year. ($4,725.00)

Peter Bent Brigham Hospital, Boston, Mass., for the further development and use of the artificial kidney as a therapeutic and investigative tool in cardiovascular and renal disease, by *John P. Merrill*. Duration 2 years. ($5,250.00)

Harvard Medical School, Boston, Mass., for the production and study of congestive heart failure in dogs by *Alfred P. Fishman*. Duration 1 year. ($525.00)

Montefiore Hospital, New York, N. Y., for the study of the mechanism of edema formation following administration of electrolytes to congestive heart failure patients, by *Abraham G. White*. Duration 1 year. ($3,255.00)

University of Rochester School of Medicine and Dentistry, Rochester, N. Y., for the study of hemodynamics and ballistocardiography, by *Herbert R. Brown, Jr*. Duration 1 year. ($2,866.50)

Cornell University Medical College, New York, N. Y., for the study of the effects of drugs on the action potential of heart muscle, by *McKeen Cattell*. Duration 1 year. ($5,565.00)

Baylor University College of Medicine, Houston, Texas, for the study of (a) the effect of increasing plasma levels of potassium on the dynamics of the circulation, and (b) the relation between the pressure events in the right and left ventricles and right auricle and the electrocardiogram, by *Russell A. Huggins*. Duration 1 year. ($3,543.75)

The University of Georgia, School of Medicine, Augusta, Ga., for the study of the effects of the adrenolytic agents on the intact cardiovascular system of the anesthetized dog when administered in the presence of sympathomimetic agents, by *Raymond P. Ahlquist*. Duration 2 years. ($2,572.50)

Cornell University Medical College, New York, N. Y., for the study of the relationship between increased activity of the adrenal cortex and posterior lobe of the pituitary gland and fluid and electrolyte retention in edema, by *Robert F. Pitts*. Duration 3 years. ($8,085.00)

University of Southern California, School of Medicine, Los Angeles, Calif., for the study of the pathogenesis of hypertension due to the substitution of hypertonic sodium chloride solutions for the drinking water, by *Douglas R. Drury and Leo A. Sapirstein*. Duration 2 years. ($8,820.00)

Presbyterian Hospital, Chicago, Ill., for the study of the identification of the conduction system of the heart, by *George M. Hass*. Duration 1 year. ($4,620.00)

Tulane University of Louisiana School of Medicine, New Orleans, La., for the study of the hemodynamic and iron storing function of ferritin, with particular reference to the kidney, by *H. S. Mayerson*. Duration 3 years. ($3,675.00)

Albany Medical College, Union University, Albany, New York, for the study of (a) chronic physiological aspects of atrial and ventricular septal defects and (b) chronic physiological aspects of mitral and aortic valvular insufficiency, by *Harold C. Wiggers*. Duration 2 years. ($5,460.00)

Columbia University College of Physicians and Surgeons, New York, N. Y., for the study of revascularization of the heart, by *Ferdinand F. McAllister*. Duration 1 year. ($3,150.00)

Mt. Sinai Hospital, New York, N. Y., for the evaluation of the role of the kidney in the pathogenesis of heart failure, by *Jonas H. Sirota*. Duration 1 year. ($3,150.00)

Yale University School of Medicine, New Haven, Conn., for the study of hemodynamic factors affecting electrolyte metabolism and the renal excretion of electrolytes, by *Allan V. N. Goodyer*. Duration 1 year. ($4,620.00)

The Children's Hospital, Boston, Mass., for the study of methods for grafting of blood vessels, by *Robert E. Gross*. Duration 1 year. ($10,500.00)

The Universtiy of Texas Medical Branch, Galveston, Texas, for the study of the role of the adrenal cortex in the pathogenesis of hypertension and associated cardiovascular lesions induced by treatment with desoxycorticosterone, by *Charles E. Hall*. Duration 1 year. ($5,250.00)

Emory University School of Medicine, Atlanta, Ga., for the study of the response of the pulmonary vascular bed to hemodynamic alterations in the systemic circulation, by *James V. Warren*. Duration 3 years. ($5,250.00)

Emory University School of Medicine, Atlanta, Ga., for the study of controlling factors in the renal maintenance of sodium balance, by *Walter H. Cargill*. Duration 1 year. ($4,725.00)

Dartmouth Medical School, Hanover, New Hampshire, for the further development and appli-

cation of electrical impedance methods to the measurement of various cardiac and circulatory problems, by *Jan Nyboer*. Duration 1 year. ($5,118.75)

Harvard Medical School, Boston, Mass., for the study of peripheral vasculature by injection techniques and the relation of pathologic findings to the clinical manifestations, by *Herrman L. Blumgart*. Duration 1 year. ($3,675.00)

The University of Illinois College of Medicine, Chicago, Ill., for the study of the relation of pituitary and adrenal cortex to experimental renal hypertension, by *George E. Wakerlin*. Duration 1 year. ($5,250.00)

Bowman Gray School of Medicine, Winston-Salem, N. C., for the study of the nature and cause of the vasoconstriction which appears in the course of perfusion of isolated organs, by *Harold D. Green*. Duration 2 years. ($4,725.00)

Western Reserve University School of Medicine, Cleveland, Ohio, to construct a recording thermometer capable of accurately registering continuously small changes in temperature associated with the heart beat in physiological and patho-physiological experimental conditions, by *Herman K. Hellerstein*. Duration 1 year. ($2,625.00)

Fels Research Institute, Antioch College, Yellow Springs, Ohio, for the application of a newly devised oxygenation apparatus to the study of experimental pulmonary and circulatory failure, by *Leland C. Clark and Frank Gollan*. Duration 1 year. ($6,195.00)

The University of Southern California, School of Medicine, Los Angeles, Calif., for the study of the chemistry of constriction of the blood vessels, by *Chester Hyman and Walter Marx*. Duration 1 year. ($3,150.00)

Ochsner Foundation Hospital, New Orleans, La., for the measurement of blood flow by recording changes in the electrical conductivity of various tissues, by *Thomas Findley*. Duration 1 year. ($4,200.00)

ANNUAL MEETING OF SOCIETY FOR VASCULAR SURGERY

The fourth annual meeting of the Society for Vascular Surgery will be held in the Terrace Room of the Fairmont Hotel, San Francisco, on Sunday, June 25, 1950. Dr. Daniel C. Elkin is President. The preliminary program lists the following papers:

Intravenous Agglutination of Erythrocytes (Sludged Blood) in Trauma, *W. G. Bigelow, M.D.*

Surgical Management of Secondary Hypersplenism, *Jere Lord, Jr., M.D.*

The Management of Popliteal Aneurysms, *J. M. Janes, M.D.*

Experimental Studies of the Frozen Homologous Aortic Graft, *Ralph A. Deterling, Jr., M.D., C. C. Coleman, Jr., M.D., and Mary Parshley, Ph.D.*

Some Experimental Aspects of Coarctation of the Aorta, *Frank Gerbode, M.D.*

The Effect of Vasodilator Drugs on the Circulation of the Extremities, *Daniel C. Elkin, M.D.* (President's Address).

Raynaud's Syndrome: A Clinical Study of Criteria for Prognosis, *Frederick Coller, M.D., and Alexander Blain, III, M.D.*

An Evaluation of the Deep Leg Veins following Thrombophlebitis, *Josephus C. Luke, M.D.*

Division of the Popliteal Vein in Deep Venous Insufficiency of the Lower Extremities, *Geza deTakats, M.D., and G. W. Graupner, M.D.*

Acute Massive Occlusion of the Venous System of the Lower Extremities, *J. Ross Veal, M.D.*

Ambulatory Venous Pressure Studies in the Post-phlebitic and other Disease States, *Paul DeCamp, M.D., J. A. Ward, Jr., M.D., R. J. Schramel, M.D., N. D. Feibelman, M.D., and Alton Ochsner, M.D.*

Experiences with Ligation and Heparin in the Prevention of Pulmonary Emboli, *Isador Ravdin, M.D., and Charles K. Kirby, M.D.*

PORTUGUESE HEART SOCIETY

An announcement has been received from Lisbon, Portugal, of the formation of the Portuguese Heart Society (Sociedade Portuguesa de Cardiologia). The President is Professor Joao Porto and Vice-Presidents are Professors Joao Cid dos Santos and Joao Cerqueira Gomes. Dr. Arsenio Cordeiro is Secretary. The address is Avenida Da Liberdade, 65-1.°, Lisbon.

This Issue Is in Honor of

JAMES BRYAN HERRICK

JAMES BRYAN HERRICK, M.D.

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FOREWORD

IT IS fitting that this special issue of a new journal devoted to the cardiovascular disorders be dedicated to our most distinguished living student of these disorders. James Bryan Herrick's reports were perhaps the single outstanding factor in creating that interest in the field which has made the new journal necessary. His career, like that of most men of lasting note in medicine, resembles Caesar's Gaul; it may be divided into three parts—the physician, the investigator, the teacher. The integrative component of these three facets is the man himself. The purpose of these lines is to mention a few of the reasons why the medical historian of the future will accord a prominent place to the accomplishments of Dr. Herrick and will place him in a firmament already enriched by such shining lights as Heberden, Withering, Corvisart, Hope, Stokes, Traube, Wenckebach, Lewis and Mackenzie.*

As a physician, Dr. Herrick has represented the rare combination of the clear scientific mind and the warm human heart. When he came to the Peter Bent Brigham Hospital as Physician *pro tem* in 1924, all of us on the house staff were impressed by these happy qualities, and my Chicago friends tell me that "Age cannot wither nor custom stale his infinite variety."

Although he has contributed extensively to the broad field of internal medicine, Dr. Herrick is best known for his descriptions of sickle cell anemia and of myocardial infarction. As regards the latter condition he was, in some degree, preceded by various other observers who from time to time made the correct diagnosis ante mortem. However, it was the carefully documented reports of Dr. Herrick with their precise description of the clinical picture which led, in time, to the general recognition of the disorder and thus gave impetus to the whole field of clinical cardiology. It was his stimulus which led Fred Smith to study the condition in animals and delineate the electrocardiographic changes. What many hold to be the finest single intellectual achievement of modern times in the field—Frank Wilson's elucidation of the electrocardiogram—came along a few years later and added further to the value of Dr. Herrick's work. The light which Dr. Herrick ignited has not obeyed Newton's law; its intensity has tended to vary not inversely but directly with the square of the distance as each new discovery begets several more.

Despite the importance of Dr. Herrick's contributions to medical knowledge one wonders whether this is his greatest accomplishment. Our future historian may well take the position that he, like Osler, is one of those rare persons whose heart has contributed more than his head. His gentleness, kindness, understanding and leadership have made him one of the outstanding teachers of our times. I have talked with many of his pupils and have encountered no sentiments other than admiration and respect coupled with affection and gratitude.

* Those readers who, like Dr. Herrick, are students of history and of literature, as well as of medicine, may well object to the omission of Queen Elizabeth. It will be recalled that on one occasion Sir Walter Raleigh is said to have climbed the side of the palace to the level of Elizabeth's chambers and to have written on her window:

"High would I climb, yet fear to fall"; and the Virgin Queen completed the couplet by writing:

"If thy heart fail thee, climb not at all."

One might therefore argue that Queen Elizabeth anticipated by three hundred years Mackenzie's immortal dictum that the test of a heart is the response to effort.

As a man Dr. Herrick is, like Dr. Osler, the embodiment of the three attributes which were called by Lord Tweedsmuir humility, humanity and humor. His high caloric scientific intellectual diet has been properly balanced by the vitamins of the classics. He is a devotee of medical history, as was first called to my attention by a delightful note received some fifteen years ago in which he pointed out that some of the observations which I had been inclined to ascribe to James Hope had been made a century previously by Raymond Vieussens. This gentle admonition was delivered in the kindest words. Although the note has been lost, memory indicates that it stated: "Isn't it interesting and fun to know that Vieussens observed some of these same things and described them so beautifully?" It is perhaps no coincidence that the greatest teachers of medicine have almost without exception been, like Dr. Herrick, individuals with an extensive training and interest in the humanities as well as in the sciences.

Men such as Dr. Herrick, with the insight into the future which comes from science, and the understanding of the past derived from the humanities, seem especially likely to achieve not only distinction from without but, more importantly, serenity from within. Such men are optimistic, and radiate their own happiness to others. They face the future with the confidence of experience and the curiosity of a youthful spirit. Those with the good fortune to know Dr. Herrick even slightly can picture his quiet chuckling as he says to himself:

"Grow old along with me! The best is yet to be,
The last of life, for which the first was made . . . ."

The Editor, Editorial Board, and Publisher of CIRCULATION consider it a great privilege and honor to dedicate this special issue to Dr. Herrick. It is quite certain that they speak for his host of friends and his countless admirers in wishing him many more years of usefulness and happiness.

Tinsley R. Harrison, M.D.

The Relationship of the Degree of Coronary Atherosclerosis with Age, in Men

By Neil K. White, M.D., Jesse E. Edwards, M.D., and Thomas J. Dry, M.B.

The amount of coronary atherosclerosis in each decade from 30 to 89 years of age, in the male, is evaluated. A large number of hearts were examined in great detail to increase accuracy. The results reveal that the degree of coronary atherosclerosis is not primarily related to age as is commonly assumed. The effect of cardiac hypertrophy on coronary atherosclerosis is also discussed.

THE LITERATURE has consistently stressed the opinion that coronary atherosclerosis, as evaluated from necropsy studies, increases in severity with advancing age.[3, 5-7] The data, forming the basis of these opinions, in most instances have been derived from necropsy protocols. As a rule, the persons concerned in recording the data for any one report are many and their interest and experience in the study of the coronary arteries vary. Thus, in any one group of cases reported there may be considerable lack of uniformity in interpretation of observations. It is evident that a study performed by one individual would yield more uniform interpretations from case to case. Accordingly, a restudy was made of the degree of coronary atherosclerosis in the hearts of 100 consecutive men from each of the decades from age 30 through 89 years; a study totaling 600 hearts.

Material and Methods

The hearts used in this study had been saved at the time of necropsy as a routine procedure without regard to whether or not cardiac disease was present. The specimens had been obtained from routine consecutive necropsies on men and represented persons dying from many and varied causes. Those dying of disease of the coronary arteries or any other disease were not excluded. One hundred hearts from each of the six decades starting with the age of 30 years were used in this study. All of the subjects were men.

A method of examination was outlined by which a complete picture of the degree of coronary sclerosis in all parts of the coronary tree could be determined. This entailed the separation of the coronary tree in each heart into the following divisions for the purpose of recording sclerosis. The left coronary artery was divided into the left main coronary stem, the anterior descending branch, and the circumflex branch. The right coronary artery was divided into the right main coronary stem, the marginal branch, and the posterior descending branch. Each of these divisions was then subdivided into proximal, middle, and distal parts, except the left main coronary stem, which is usually 1 to 3 cm. in length and is too short for subdivision. This division of the coronary system is pictured in figure 1.

Each of the 600 hearts had, then, sixteen subdivisions of the coronary arteries which were separately evaluated for the degree of sclerosis. Cross sections were made with a sharp knife at 3-mm. intervals from the ostia to the terminal pericardial branches. Each section was carefully examined and its lumen was visualized. This method, it was felt, would provide an accurate picture of the amount of sclerosis for the entire coronary system.

Abridgment of thesis submitted by Dr. White to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

The actual grading was on a basis of Grade 1 (minimal sclerosis) to Grade 4 (complete atherosclerotic closure of the lumen).

The microphotographs shown in figure 2 are average selections from each of the four grades of sclerosis as standardized for this study.

The maximal degree of sclerosis as found in each of the sixteen segments was the recorded sclerosis for that segment.

The average grade of sclerosis in this segment increases from Grade 1.58 during the age period of 30 through 39 years to an average of Grade 2.42 during the age period of 50 through 59 years. The greatest amount of sclerosis was found in the sixth decade with a slight decrease in subsequent decades.

The findings in the anterior descending branch of the left coronary artery are presented in figure 4. In general the curves are similar to those found for the left main coronary stem. The proximal segment of the anterior descending branch showed a higher average grade of sclerosis than any of the other fifteen segments studied. The age period in which the maximal sclerosis was present was again the 50-year through 59-year period, with less sclerosis in the succeeding decades. In every age period the average sclerosis in the middle segment was less than in the proximal, and the average sclerosis in the distal was less than in the middle segment.

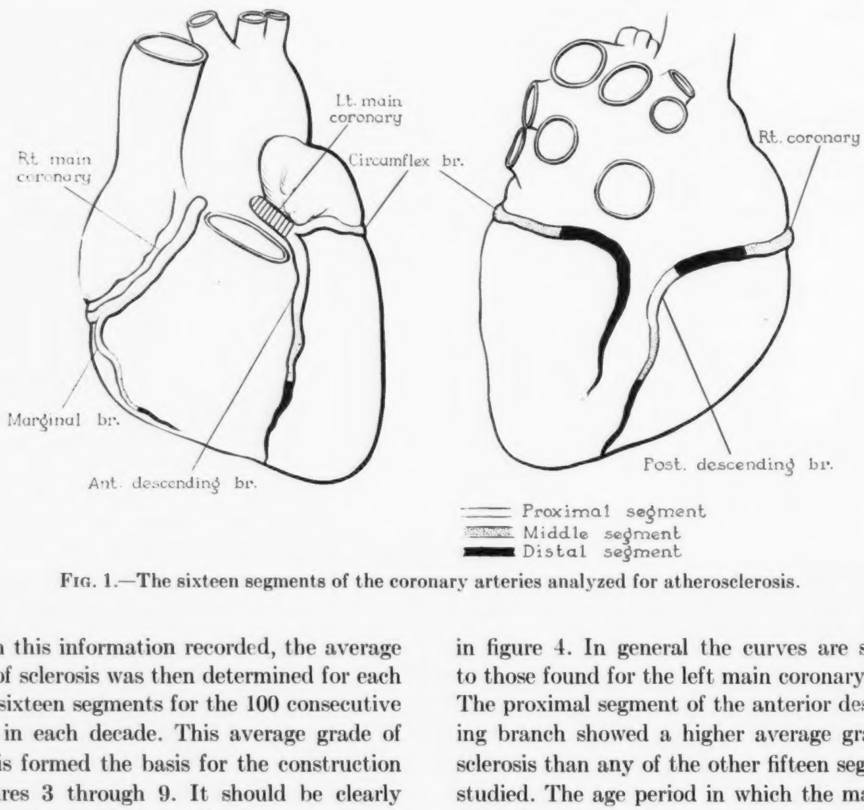

FIG. 1.—The sixteen segments of the coronary arteries analyzed for atherosclerosis.

With this information recorded, the average grade of sclerosis was then determined for each of the sixteen segments for the 100 consecutive hearts in each decade. This average grade of sclerosis formed the basis for the construction of figures 3 through 9. It should be clearly understood that these figures do not represent the changes in degree of atherosclerosis in an *individual heart* as age increases, but are the average results obtained from the study of necropsy material.

Figure 3 presents the findings in the left main coronary stem from the ostium in the left aortic sinus to its division into the anterior descending and circumflex branches. This segment is seldom more than 3 cm. in length.

Figure 5 presents the findings in the circumflex branch of the left coronary artery. The results are similar to those for the anterior

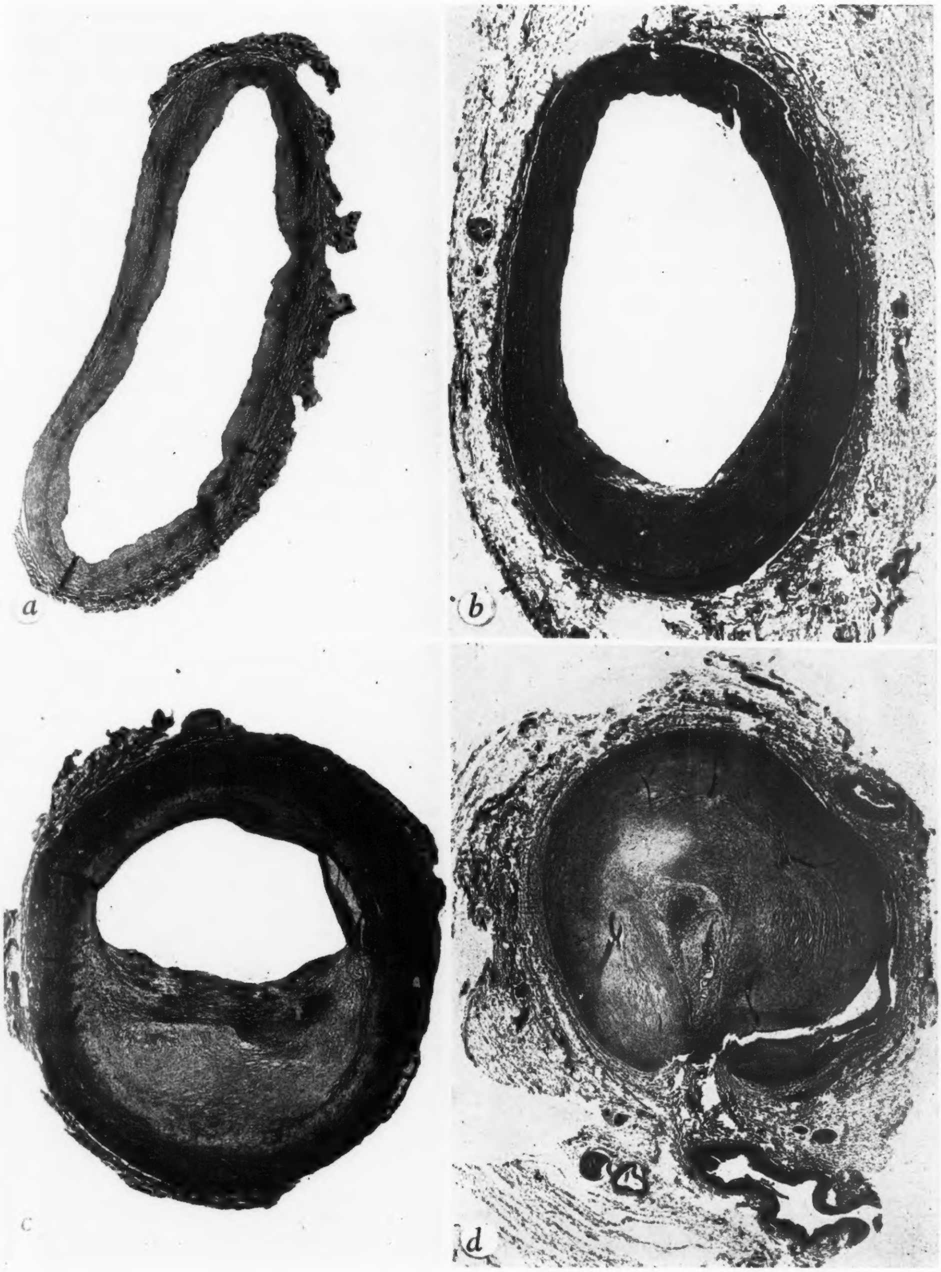

FIG. 2.—Examples of the grading of sclerosis in coronary arteries: *a*, Grade 1 (×30); *b*, Grade 2 (×22); *c*, Grade 3 (×15); *d*, Grade 4 (×15).

descending branch, except that the average grade of sclerosis was somewhat lower. The decade having the most sclerosis was the 50-year through 59-year age group. The average

sclerosis in the proximal segment of the circumflex branch in this decade was Grade 2.68 as compared to Grade 3.00 for the anterior descending branch. As in the case of the latter branch, the middle and distal segments of the circumflex branch showed less severe sclerosis than did the proximal segment.

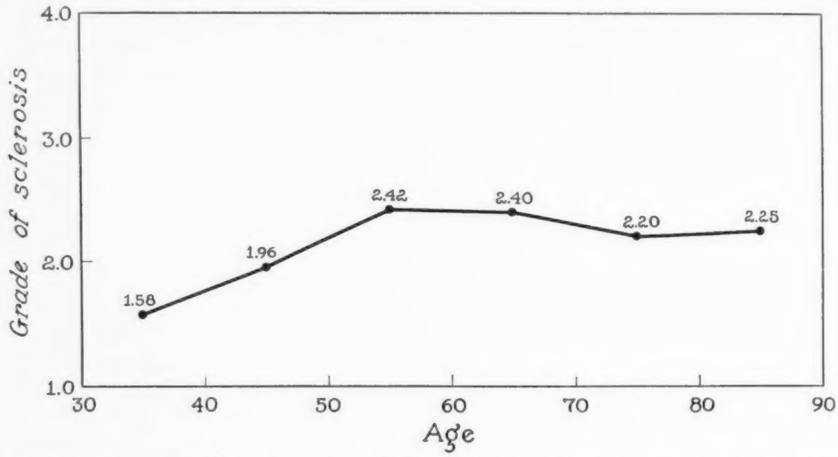

FIG. 3.—The average grade of coronary sclerosis in the left main coronary stem (proximal to the point of division into the anterior descending branch and the circumflex branch) for 600 hearts according to decades studied.

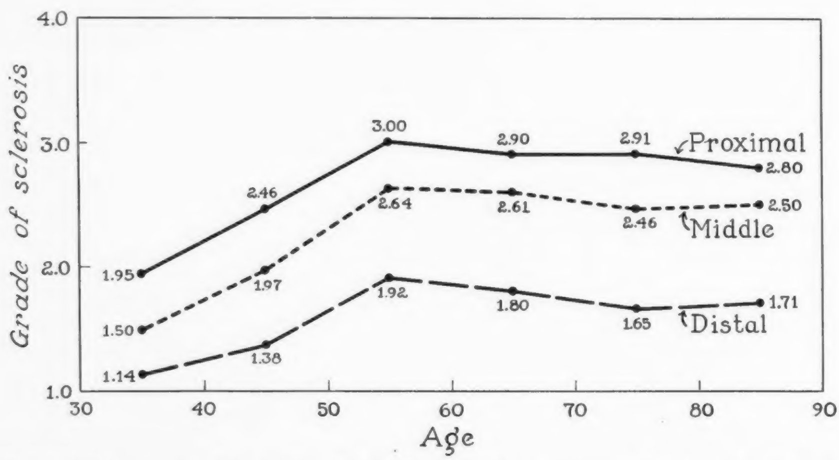

FIG. 4.—The average grade of coronary sclerosis in the three segments of the anterior descending branch of the left coronary artery for 600 hearts according to decades studied.

Figure 6 presents the findings in the right main coronary stem. In this instance, the right main coronary stem represents all of the right coronary artery from the ostium in the right aortic sinus to the posterior longitudinal sulcus, at which point the right coronary artery continues as the posterior descending branch. The curves in general are similar to those noted in the left coronary artery and its major branches. The maximal grade of sclerosis was present in the 50-year through 59-year group. The segment of the right main coronary stem having the greatest degree of sclerosis was the middle

segment—or more specifically, that segment extending from a point approximately 3.5 cm. from the ostium to another point about 7 cm. from the ostium. It should be noted that the

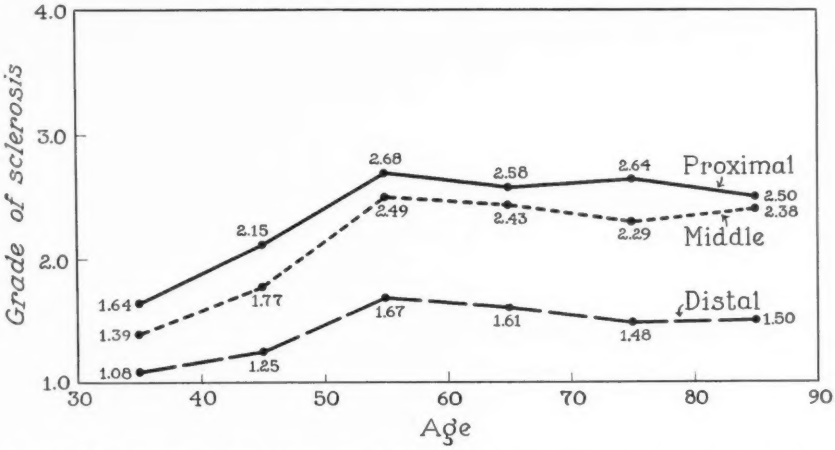

FIG. 5.—The average grade of coronary sclerosis in the three segments of the circumflex branch of the left coronary artery for 600 hearts according to decades studied.

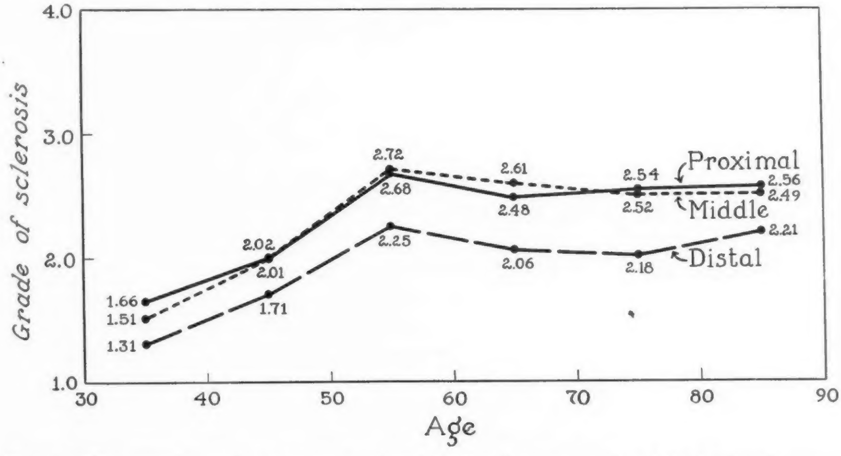

FIG. 6.—The average grade of coronary sclerosis in the three segments of the right main coronary stem for 600 hearts according to decades studied.

degree of sclerosis found was only a little less than in the anterior descending branch of the left coronary artery. The general pattern of degree of sclerosis was identical. It would seem that there are no inherent differences in the development of atherosclerosis in the left and right coronary arteries.

Figure 7 presents the findings in the marginal branch of the right coronary artery. This is usually the smallest of all the so-called main branches of the coronary arteries, and correspondingly had the least degree of sclerosis. The maximal amount of sclerosis was found in the proximal segment of this artery in the 50-year through 59-year age group.

Figure 8 presents the results of the study of the posterior descending coronary artery. There were no variations noted from the previous findings. This artery is slightly larger than the

right marginal branch and has a higher average grade of sclerosis. The average grade of sclerosis in the last two arteries named never reaches more than a moderate amount (Grade 2). This is not a surprising finding, inasmuch as both the marginal and posterior descending arteries are relatively small branches, and merely follow the general trend of the grade of sclerosis decreasing toward the distal portion of the artery. Among the 600 hearts of this study the posterior descending coronary artery represented the terminal portion of the left circumflex artery in 45 cases; in the other 555 cases this artery represented the terminal portion of the right coronary artery.

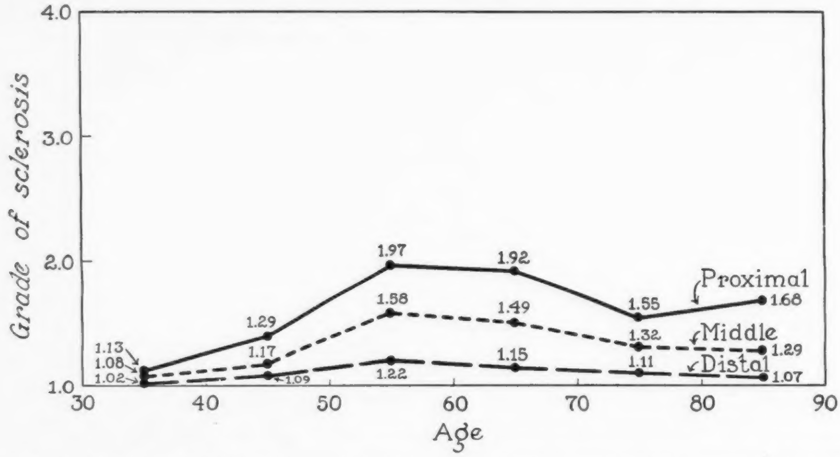

FIG. 7.—The average grade of coronary sclerosis in the three segments of the marginal branch of the right coronary artery for 600 hearts according to decades studied.

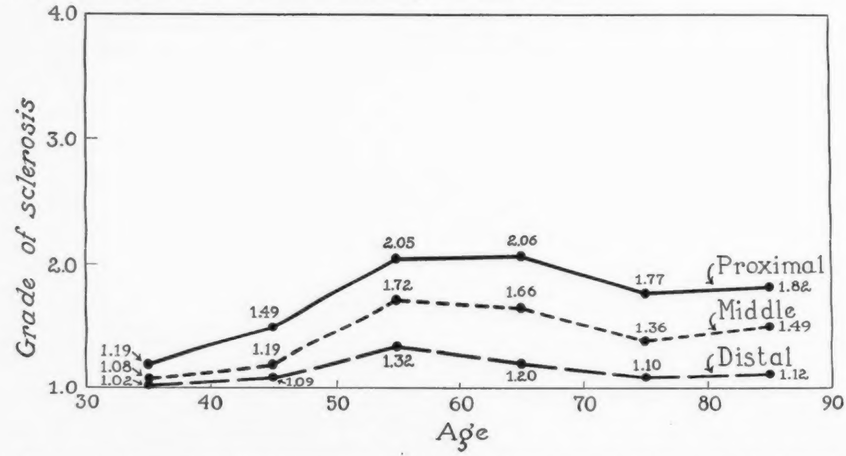

FIG. 8.—The average grade of coronary sclerosis in the three segments of the posterior descending coronary artery for 600 hearts according to decades studied.

Figure 9 is a composite to compare the maximal degree of sclerosis found in the six main branches of the coronary arteries. The curves show an average grade of sclerosis slightly greater than those noted in the previous figures. This is readily understood, inasmuch as the greatest amount of sclerosis found along the entire course of the branch, whether in its proximal, middle, or distal segment, was the grade used to determine these averages.

The main points emphasized by this repre-

sentation are that a careful examination of the coronary arteries reveals a rather severe degree of sclerosis at some point along the main arteries after the age of 49 years, and that the degree of sclerosis in the right main coronary stem and in the circumflex branch of the left coronary artery is only slightly less than that in the anterior descending branch.

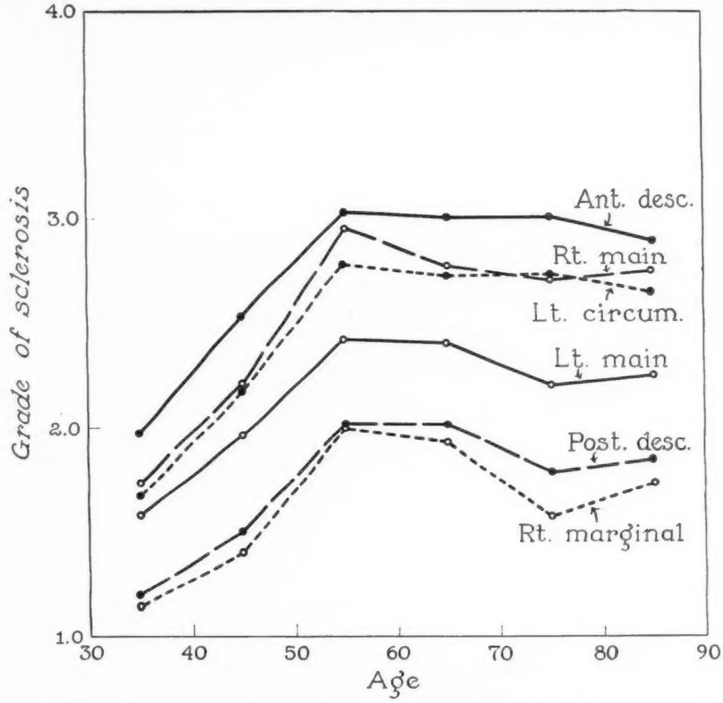

FIG. 9.—The average of the greatest degree of sclerosis found in each of the complete branches of the coronary arteries (combining findings of proximal, middle, and distal segments) for each decade.

In figure 10 the degree of sclerosis in each decade is studied from a different viewpoint. We wished to find the percentage of hearts in each decade in which there was a severe involvement of the coronary arteries. By our method of grading, this would include all coronary arteries with a grade of sclerosis of 3 or more (see fig. 2). The line in figure 10 marked "right" gives the percentage of hearts, in each decade, in which there was sclerosis of Grade 3 or more at some point in the right coronary artery or its ramifications. The line marked "left" shows the percentage of hearts, in each decade, in which there was sclerosis of Grade 3 or more at some point in the left coronary artery or its ramifications. The top line, marked "either," gives the percentage of hearts, in each decade, in which there was found sclerosis of Grade 3 or more at any point in either coronary artery. This top curve is not a summation of "right" and "left" but actually represents all of the hearts in which there was sclerosis of Grade 3 or more in the left coronary artery *plus* the relatively few hearts in which there was sclerosis of Grade 3 or more in the right coronary artery with less than Grade 3 sclerosis in the left coronary artery.

In this regard it was found that 11 per cent of the hearts in the 50-year through 59-year period had sclerosis of Grade 3 or more in the right coronary artery, with less than Grade 3 sclerosis in the left coronary artery. Clawson[1] found this relationship in only 1 per cent of the 928 cases of coronary sclerosis of all ages that he reported in 1939.

According to Clawson,[1, 2] hypertension pre-

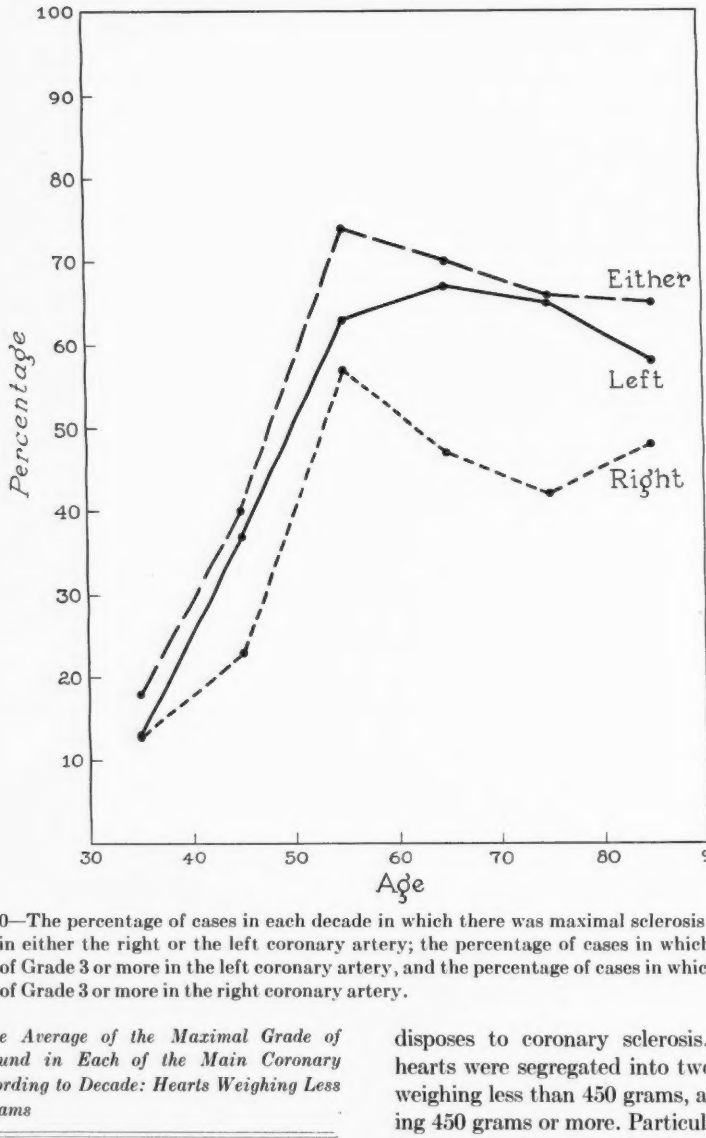

FIG. 10—The percentage of cases in each decade in which there was maximal sclerosis of Grade 3 or more in either the right or the left coronary artery; the percentage of cases in which there was sclerosis of Grade 3 or more in the left coronary artery, and the percentage of cases in which there was sclerosis of Grade 3 or more in the right coronary artery.

TABLE 1.—*The Average of the Maximal Grade of Sclerosis Found in Each of the Main Coronary Arteries According to Decade: Hearts Weighing Less Than 450 Grams*

No. of hear	76	60	63	61	61	71
Age, years	30–39	40–49	50–59	60–69	70–79	80–89
Left main stem	1.60	1.94	2.37	2.35	2.15	2.27
Anterior descending	1.91	2.47	2.94	2.95	2.94	2.85
Circumflex	1.65	2.09	2.66	2.63	2.67	2.56
Right main stem	1.68	2.02	2.82	2.64	2.60	2.75
Marginal	1.12	1.21	1.90	1.86	1.56	1.69
Posterior descending	1.18	1.37	2.06	1.98	1.71	1.77

disposes to coronary sclerosis. Therefore, all hearts were segregated into two groups—those weighing less than 450 grams, and those weighing 450 grams or more. Particularly in the male heart, when long-standing hypertension exists, the great majority of hearts will weigh more than 450 grams. Rather than analyze all sixteen segments, we took the maximal degree of sclerosis found in each of the five main branches of the coronary arteries plus the main stem of the left coronary artery for each heart. The average of the maximal grade of atherosclerosis found for each artery and for each decade is given in tables 1 and 2.

The hearts weighing 450 grams or more consistently showed a slightly greater degree of coronary sclerosis than those weighing less than 450 grams, but the actual amount of sclerosis is seldom more than 10 per cent greater in the hearts weighing 450 grams or more than in those weighing less than 450 grams for corresponding coronary arteries and decades. It is certain that the myocardium of the hypertrophied heart is affected to a much greater degree than indicated by the slightly increased amount of sclerosis, inasmuch as its oxygen demand increases as hypertrophy develops. Therefore, the hypertrophied heart will succumb to coronary arterial disease before the heart of the normal size if both have an equal grade of coronary sclerosis. As mentioned previously, the hearts weighing 450 grams or more showed about 5 to 10 per cent greater degree of sclerosis than the hearts weighing less than 450 grams. This would further accentuate the myocardial anoxemia.

TABLE 2.—*The Average of the Maximal Grade of Sclerosis Found in Each of the Main Coronary Arteries According to Decade: Hearts Weighing 450 Grams or More*

No. of hearts	24	37	34	38	38	26
Age, years	30–39	40–49	50–59	60–69	70–79	80–89
Left main stem	1.56	2.03	2.51	2.48	2.24	2.19
Anterior descending	2.10	2.71	3.12	3.11	3.11	3.10
Circumflex	1.77	2.38	2.96	2.87	2.82	2.82
Right main stem	1.93	2.55	3.11	2.97	2.90	2.76
Marginal	1.20	1.69	2.22	2.06	1.70	1.87
Posterior descending	1.30	1.71	2.17	2.21	1.97	2.05

Comment

The main purpose of this study was to determine whether the average grade of coronary sclerosis, as observed in necropsy material, increases progressively with age, as has been repeatedly stated in the literature. The present series failed to substantiate this contention. It was found that the average grade of sclerosis in each of the sixteen subdivisions of the coronary tree for which an evaluation was made, followed a similar pattern when related to age. In all instances the average grade of sclerosis rose steadily with age from the first period studied, 30 through 39 years of age, to a maximal rather severe average grade of sclerosis in the 50-year through 59-year age group. Beyond this age group the average grade of sclerosis did not increase.

In our series in 18 per cent of the hearts in the 30-year through 39-year age group sclerosis of Grade 3 or more affected some part of the coronary tree. French and Dock[4] investigated 80 cases of fatal coronary disease in soldiers between the ages of 20 and 36 years. Seventy of the 80 patients died within a few minutes after the onset of the attack. In these hearts adequate collateral circulation had not as yet developed. Sudden death of this nature is much less common after the age of 50 years than before that age. This definitely suggests that the collateral coronary circulation develops as the degree of sclerosis increases and according to our findings would be well established by the sixth decade.

Conclusions

1. Six hundred hearts, consisting of a series of 100 consecutively chosen hearts of men in each of the six decades from 30 through 89 years of age, were thoroughly examined for the amount of coronary sclerosis. It has been shown that the degree of coronary sclerosis in necropsy material is not linearly related to age, but increases rapidly in the 30-year through 49-year age period, reaches a maximum in the 50-year through 59-year age group, and thereafter remains at a fairly constant level.

2. Beyond the age of 49 years, the average man at the time of death has a rather severe degree of coronary atherosclerosis—amounting to a Grade 3 sclerosis (on a basis of Grade 1 to Grade 4) at some point in both the left and right coronary arteries.

3. Hypertension—as revealed by myocardial hypertrophy—is not a primary factor in the production of coronary atherosclerosis. The average grade of sclerosis in the hearts weighing 450 grams or more was less than 10 per cent greater than in the hearts weighing less than 450 grams.

4. The pattern of development of sclerosis in the right coronary artery is similar to that

found in the left coronary artery, and does not seem to justify the conclusion that there are inherent differences in the manner of development of sclerosis in the two arteries. The proximal segment of the anterior descending branch of the left coronary artery had the highest average grade of sclerosis of any of the sixteen segments studied. However, the degree of difference between this segment and corresponding segments of the right main coronary stem was not striking.

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The Use of Tetraethylammonium Chloride as a Vasodilator in Peripheral Vascular Disease; Its Effect on Sympathectomized Extremities

By Theodore B. Massell, M.D., William E. Adolph, M.D., and James B. French, M.D.

The thermometric and plethysmographic response to Etamon administration was studied in 13 patients with peripheral vascular disease, comparing it with that of procaine injection into the sympathetic ganglia. The administration of Etamon caused an average temperature rise of 7 degrees F. and a pulse volume increase of 1.3 cu. mm. per 5 cc. of part. Procaine block resulted in a temperature rise of 13.5 degrees F. and a pulse volume increase of 5.5 cu. mm. Etamon was given to 11 vascular patients after sympathectomy and caused an average temperature rise of 0.5 degrees F. in the sympathectomized extremities, while the pulse volume actually decreased by an average of 0.7 cu. mm. per 5 cc. of part.

EARLY reports[1, 4, 11] on the effect of tetraethylammonium chloride (Etamon) on man seemed to indicate that it was more effective in producing dilation of the vessels of the extremities than was procaine injection of the sympathetic ganglia. However, experiments more recently described[5, 6, 9, 10] cast doubt on the efficacy of tetraethylammonium chloride as a peripheral vasodilator. Moreover, we have been unable to find any published data on the effect of Etamon on the peripheral circulation of a sympathectomized extremity.

The purpose of this report is: (1) to compare the effect of procaine sympathetic block with that of Etamon on the terminal vessels of the extremities in patients with peripheral vascular disease and (2) to determine the effect of Etamon on the peripheral circulation in sympathectomized extremities.

Method and Results

Experiment 1. Thirteen patients with peripheral vascular affections were studied. Six had occlusive arterial disease and 7 had vasospastic disorders. In 3 patients the disease involved chiefly the upper extremity; in the remainder the leg was the affected part. Etamon was administered intravenously as 5 cc. of a 10 per cent solution (500 mg.). Sympathetic block was performed by the Homans technic,[8] injecting 15 cc. of a 2 per cent procaine solution into the area of the second lumbar or the stellate ganglion.

Thermometric and plethysmographic recordings were obtained simultaneously from terminal portions of three extremities. The skin temperatures were recorded by a Leeds and Northrop micromax with thermocouples attached to the skin of the toes and fingers. The volume of pulse deflection per 5 cc. of part was measured by the Burch[2] pneumoplethysmograph. All observations were made in a cool, comfortable room with the patient resting in the horizontal position and shielded from psychic disturbances. Recordings were simultaneous and continuous throughout the period of measurement. An interval of twenty-four to seventy-two hours was allowed to elapse between the administration of Etamon and the procaine block. Comparative measurements were made on each patient at the same room temperature and in the same relation to meals and other daily activities. The same digits were used in each patient for comparative measurements throughout the experiment.

In the 13 patients tested, the temperature of the tip of the affected extremity reached an average of 84 F. after the administration of

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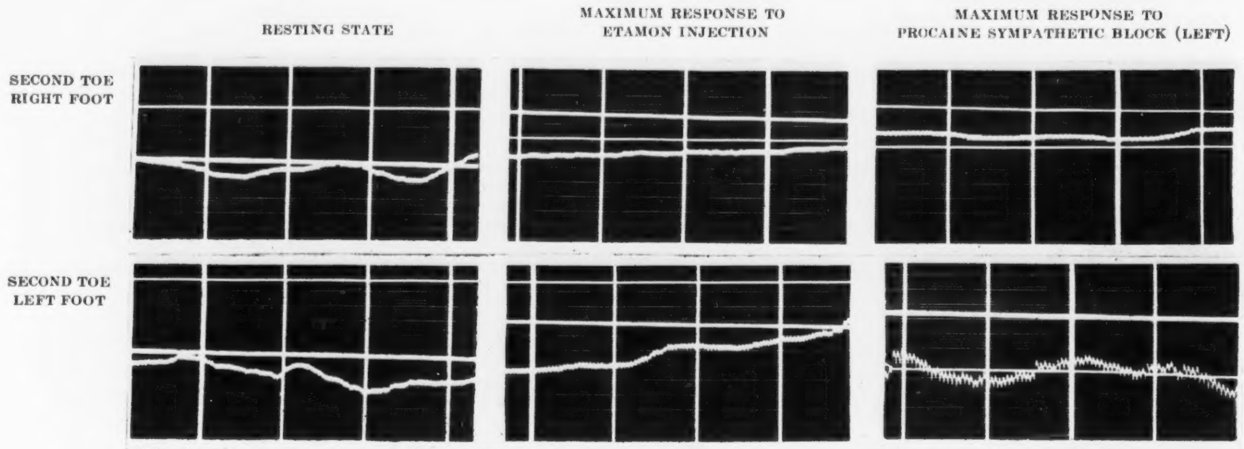

FIG. 1.—Comparison of Etamon and procaine block in thromboangiitis obliterans. Plethysmograms made simultaneously from the second toe of each lower extremity in a patient with marked peripheral arterial occlusion. In the resting state the pulse amplitude was slightly greater on the left than on the right. After the injection of Etamon, there was essentially no change on the right and a slight increase in pulse volume on the left. After a left lumbar sympathetic block there was a marked increase in the pulse amplitude in the blocked extremity.

etamon, a rise of 7.0 degrees; after sympathetic block the average was 90.5 F., a rise of 13.5 degrees. There was a striking difference in pneumoplethysmographic response. The drug caused an increase in pulse amplitude of only 1.3 cu. mm. per 5 cc. of part, whereas procaine injection resulted in an increase of 5.5. cu. mm. per 5 cc. of part. The figures for the individual patients are given in table 1.

An analysis of these individual results reveals that the temperature increase produced by Etamon injection was less in every case except one than the increase caused by sympathetic block. In only one patient (patient 12) did Etamon administration cause a greater increase in pulse amplitude than did procaine injection; in another patient (patient 13) both vasodilators caused the same pulse volume increase. In a third patient (patient 4) neither vasodilator agent affected the pneumoplethysmogram. However, in the other 10 patients the sympathetic ganglion block was considerably more effective in increasing the pulse amplitude than was Etamon. The difference was especially marked in patients 5 and 6 in whom the ratios were 11 to 1 and 73 to 1, respectively.

Figure 1 shows the difference in plethysmographic response to these two vasodilators in a patient with thromboangiitis obliterans.

Experiment 2. Eleven patients who had had unilateral sympathectomy were studied; one had upper thoracic sympathectomy, 2 thoracolumbar, and 8 lumbar (table 2). Four of these patients had previously been studied in the first series. Ten days to three weeks after operation, thermometric and plethysmographic tracings were made simultaneously on the sympathectomized and on the intact contralateral extremity before and after the intravenous administration of 500 mg. of tetraethylammonium chloride. Etamon caused an average rise of temperature of 7.2 degrees F. in the intact extremity, 0.5 degree F. in the sympathectomized extremity. The average increase in pulse amplitude on the intact side was 1.2 cu. mm., while on the sympathectomized side there was a *decrease* in pulse amplitude, averaging 0.7 cu. mm.

A consideration of the individual results reveals that the temperature rise in the sympathectomized extremity was over 1 degree in only one patient and was less than 0.5 degree in 6 patients. Only 2 patients exhibited an increased pulse amplitude on the sympathecto-

TABLE 1.—*Skin Temperature and Plethysmographic Pulse Volume after Administration of Etamon and after Sympathetic Block*

Patient No.	Diagnosis	Skin Temperature (in Degrees Fahrenheit)					Plethysmographic Pulse Volume (cu. mm.)					
		Resting	After Etamon	Increase Due to Etamon	After Block	Increase Due to Block	Resting	After Etamon	Increase Due to Etamon	After Block	Increase Due to Block	
1	Thromboangiitis obliterans	78.0	84.5	6.5	89.0	11.0	2.0	2.7	0.7	4.0	2.0	Leg
2	Acute thrombophlebitis	74.5	76.0	1.5	91.0	16.5	1.0	2.2	1.2	3.3	2.3	Leg
3	Chronic thrombophlebitis	72.0	84.0	12.0	92.0	20.0	1.0	6.8	5.8	18.0	17.0	Leg
4	Thromboangiitis obliterans	80.0	86.0	6.0	89.0	9.0	0	0	0	0	0	Leg
5	Acrocyanosis	73.0	91.5	18.5	92.5	19.5	3.5	4.0	0.5	9.0	5.5	Arm
6	Raynaud's syndrome	75.5	77.5	2.0	93.5	16.0	0	0.3	0.3	22.0	22.0	Arm
7	Arteriosclerosis obliterans	78.0	85.5	7.5	87.0	9.0	0.2	1.5	1.3	2.0	1.7	Leg
8	Thromboangiitis obliterans	78.0	93.0	15.0	89.5	11.5	3.5	4.5	1.0	8.5	4.0	Leg
9	Thromboangiitis obliterans	78.5	82.0	3.5	93.5	15.0	0.5	2.0	1.5	9.0	7.5	Leg
10	Posttraumatic reflex dystrophy	82.0	84.5	2.5	93.0	11.5	2.5	1.0	−1.5	5.5	3.0	Arm
11	Thromboangiitis obliterans	76.0	77.0	1.0	89.5	13.5	1.0	1.3	0.3	1.5	0.5	Leg
12	Posttraumatic reflex dystrophy	81.0	88.0	7.0	91.5	10.5	1.0	3.5	2.5	3.0	2.0	Leg
13	Trench foot	75.0	83.0	8.0	89.5	14.5	3.0	6.0	3.0	6.0	3.0	Leg
Average		77.0	84.0	7.0	90.5	13.5	1.5	2.8	1.3	7.0	5.5	

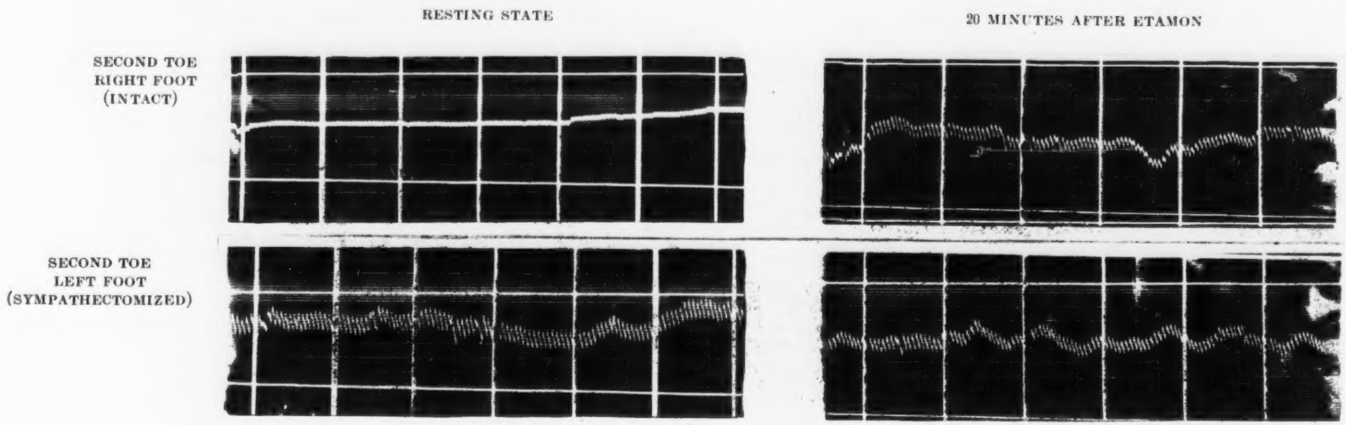

FIG. 2.— Effect of Etamon on the intact and sympathectomized extremity in thromboangiitis obliterans. Plethysmographic tracings of the second toe of the intact right foot and of the sympathectomized left foot. On the left is seen the marked difference in pulse volume which followed left lumbar sympathectomy. After the administration of Etamon there was a large increase in amplitude of the pulse on the intact extremity while there was a decrease in pulse amplitude on the sympathectomized side.

mized side following the administration of Etamon: 0.2 cu. mm. in patient 17 and 1.2 cu. mm. in patient 19. Neither of these patients had vascular disease of their sympathectomized extremities. In patient 17 the operation was performed to relieve an unexplained causalgia-like pain without any associated vascular disturbance. Sympathetic section was performed in patient 19 in an attempt to increase the circulation in an area of radiation necrosis by causing a vasodilation in an otherwise normal followed by a definite decrease in pulse amplitude varying from 0.3 cu. mm. to 5.0 cu. mm. with an average value of 1.4 cubic millimeters.

Figure 2 shows a typical plethysmogram illustrating the difference in effect of tetraethylammonium chloride on an intact and on a sympathectomized extremity in a patient with thromboangiitis obliterans.

It was also noted that in contrast to the observations of Burch and his associates[3] the frequency of alpha deflections in the

TABLE 2.—*Skin Temperature and Plethysmographic Pulse Volume in Intact and Sympathectomized Extremity before and after Etamon Injection*

Patient No.	Diagnosis	Skin Temperature (in Degrees Fahrenheit)						Plethysmographic Pulse Volume (cu. mm.)					
		Intact Extremity			Sympathectomized Extremity			Intact Extremity			Sympathectomized Extremity		
		Resting	After Etamon	Temperature Rise	Resting	After Etamon	Temperature Rise	Resting	After Etamon	Pulse Volume Increase	Resting	After Etamon	Pulse Volume Increase
4	Thromboangiitis obliterans	78.5	84.5	6.0	90.0	90.0	0	0	3.5	3.5	0	0	0
8	Thromboangiitis obliterans	85.0	93.5	8.5	92.5	93.0	0.5	7.5	7.0	−0.5	9.5	4.5	−5.0
12	Posttraumatic reflex dystrophy	81.0	91.0	10.0	91.0	91.0	0	2.0	4.0	2.0	7.5	6.0	−1.5
13	Trench foot	83.5	91.0	7.5	87.5	89.0	1.5	3.0	5.0	2.0	5.5	5.0	−0.5
14	Thromboangiitis obliterans	78.5	82.0	3.5	81.0	82.0	1.0	0.5	0.7	0.2	0	0	0
15	Essential hypertension	80.5	88.5	8.0	88.5	88.5	0	2.0	2.2	0.2	3.0	2.5	−0.5
16	Essential hypertension	77.5	80.0	2.5	89.5	89.5	0	2.5	3.0	0.5	4.5	4.0	−0.5
17	Posttraumatic reflex dystrophy	79.5	86.0	6.5	87.0	89.0	2.0	2.0	2.7	0.7	2.5	2.7	0.2
18	Arteriosclerosis obliterans	81.5	89.0	7.5	81.0	81.5	0.5	2.2	2.7	0.5	1.0	0.7	−0.3
19	Postradiation ulcer	80.0	84.0	4.0	92.5	92.5	0	2.5	3.5	1.0	4.0	5.2	1.2
20	Thromboangiitis obliterans	74.5	90.0	15.5	90.5	90.5	0	2.0	5.5	3.5	7.0	5.5	−1.5
Average		80.0	87.2	7.2	88.3	88.8	0.5	2.4	3.6	1.2	4.0	3.3	−0.7

limb. Patient 14 had advanced Buerger's disease involving both lower extremities. Sympathectomy was performed to bring about localization of a spreading gangrene of the toes. Even though the operation achieved its objective, there was no discernible arterial pulsation in the plethysmogram of either foot either before or after the administration of Etamon. However, in all seven patients with peripheral vascular disease and with a measurable digital pulse, administration of Etamon was plethysmographic tracing was not decreased by sympathectomy. In 6 patients the alpha waves were equal in frequency in the sympathectomized and in the intact limb, while in 5 patients the alpha deflections were more numerous on the sympathectomized side. Apparently the removal of the sympathetic nerve supply to the extremity did not abolish these deflections and in about half the patients increased their frequency. The removal or the preservation of the first lumbar ganglion (in

lumbar sympathectomies) did not seem to influence these results.

Discussion

Although the actual blood flow was not measured it has been demonstrated[7] that the rhythmic volume changes recorded with each heart beat are attributable to the volume of blood flowing into that particular part. While the plethysmographic and thermometric findings were approximately corroborative, there were significant differences, especially in the studies of the sympathectomized extremities. Thus the injection of Etamon was followed by a slight increase in surface temperature of the sympathectomized limb while the pulse amplitude was diminished. Inasmuch as the skin temperature may be increased by the opening of the cutaneous arteriovenous shunts without any improvement in the circulation, the change in pulse amplitude may be regarded as a more accurate indicator of the circulatory response in the limb.[7]

Both the plethysmographic and the thermometric response to Etamon were markedly less than to procaine sympathetic block and indicated the limitation of the drug as a diagnostic or therapeutic agent in peripheral vascular disease. The explanation may be found in the fact that tetraethylammonium chloride causes a generalized vasodilation. Unless the blood volume or cardiac output is increased the expansion of the vascular bed in an extremity may result in very little increase of blood flow to that extremity if there is a simultaneous expansion of the vascular bed throughout the rest of the body. When there is organic occlusion of the arteries of a limb the vascular bed is likely to be limited in its ability to expand. On the other hand, the general vasodilation produced by such a drug as Etamon often results in a drop in blood pressure and in cardiac output which may nullify the effect of the limited augmentation of the local vascular bed. Thus, in 6 patients in the first series in whom there was occlusive arterial disease the average increase in plethysmographic pulse amplitude was only 0.8 cubic millimeters. It is apparent that this limited response to Etamon was not due merely to the lack of expansibility of the vessels in the diseased limb since procaine block caused an average pulse increase of 2.6 cu. mm. in these same 6 patients. These mechanisms have previously been discussed in part by DeBakey and associates.[6]

The effect of Etamon on a sympathectomized limb is dependent upon a number of factors. Thus additional dilation of the local vascular bed might occur if sympathetic denervation were incomplete, if there had been regeneration of the vasomotor fibers, if the blood vessels were maintained in a state of constriction by some humoral mechanism (e.g., sensitivity to circulating adrenaline). In this study the observations were made too soon after sympathectomy to have been influenced by regeneration of the sympathetic fibers or by sensitivity of the vessels to adrenaline.[13] Four of the eight lumbar sympathectomies consisted of the removal of the entire lumbar chain from the first to the fourth lumbar ganglion, inclusive, and hence should have resulted in reasonably complete denervation of the vascular bed of the involved extremities.[14] On the other hand, the other four lumbar ganglionectomies spared the first lumbar ganglion, while in both thoracolumbar sympathectomies the third and fourth lumbar ganglia were left intact.

By reflex heating we were able to demonstrate that the lower extremity was completely sympathectomized in each of the 2 patients who had thoracolumbar sympathectomy. However, in this experiment the patients who had lumbar sympathectomies were not tested by reflex heat, so that it is possible that the denervation of the vascular bed might not have been complete in some patients in whom the first lumbar ganglion was left intact. The 2 patients who manifested a rise in skin temperature of more than 1 degree after the injection of Etamon were both young men in whom the first lumbar ganglion had been spared. It is possible that this thermal response to the drug represents the reaction of limbs which had not been completely freed of all vasomotor nerve fibers.

On the other hand, the administration of tetraethylammonium chloride causes a widespread dilation of the entire vascular bed, so that much of the circulating blood is diverted

to other parts of the body. In patients with peripheral vascular disease this borrowing-lending effect more than outweighs any slight augmentation in the local vascular bed of the sympathectomized limb. As a result, Etamon administration was followed by a decrease in the plethysmographic pulse amplitude in those patients in whom sympathectomy had been performed because of a vascular disease. A slight augmentation of the digital pulses was observed after the administration of the drug in only 2 patients in whom there was no vascular disease and in whom sympathectomy had not included the first lumbar ganglion.

The clinical significance of these observations lies in the effect of general vasodilators on the peripheral circulation after sympathectomy performed because of vascular disease. The use of a general vasodilator in the treatment of peripheral arterial disease after the performance of a sympathectomy might be considered either for the purpose of securing an increased amount of blood flow in the sympathectomized extremity or for the treatment of less severe vascular disease in the extremities not subjected to this operation. However, in our series the small increase in pulse volume produced by Etamon in the intact extremities hardly seemed to justify the decrease in pulse volume in the contralateral sympathectomized limbs. A similar diminution of pulse amplitude has been observed in the sympathectomized extremity after reflex heating[7] and after the administration of Priscoline.[12] Thus the use of general vasodilators is contraindicated after sympathetic denervation undertaken for treatment of vascular disease since these agents are likely to cause a decrease rather than an increase in blood flow in the sympathectomized extremity.

Conclusions

1. Tetraethylammonium chloride is considerably less effective than procaine sympathetic block as a peripheral vasodilator, so that its use is limited as a diagnostic or therapeutic agent in patients with vascular disease of the extremities.

2. Tetraethylammonium chloride does not increase and may decrease the circulation in the sympathectomized extremity in the presence of peripheral vascular disease and should not be used in the therapy of such patients.

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Recording and Visual Oscillometry by a New Standardized Technic

By Julius A. Oshlag, M.D.,† and A. Wilbur Duryee, M.D.

Oscillometry offers knowledge of clinical importance, yet its value in presently used apparatus has recently been questioned. The criticisms include shifting base line, parallax in visual reading, aging of rubber parts with consequent loss of elasticity, friction and inertia of writing mechanisms, and failure to standardize. The method suggested below obviates these defects.

THE CLINICAL oscillometer measures the expansion of a segment of an extremity occasioned by the systolic inflow of blood, when that segment is subjected to various degrees of pressure. It has been stated that plethysmographic results represent the ultimate circulation while the oscillometer deals with the penultimate circulation.[2] While total or ultimate flow cannot be determined with the oscillometer as yet, comparison of the systolic expansion of various segments of an extremity and of identical segments of the contralateral extremity offers clinical knowledge difficult to gain by other means.

Various investigators have questioned the value of the oscillometer in recent years. We believe that this has been the result of certain defects found in oscillometric apparatus available up to this time. In visually read oscillometers the frequent shifting of the base line of the moving needle, and to a lesser extent the phenomenon of parallax, make accurate reading extremely difficult. Standardization has not hitherto been provided for. Gross inaccuracy thus appears when comparison of readings taken on two different instruments is attempted. Indeed, inaccuracy is to be anticipated in comparison of readings taken on the same piece of apparatus when sufficient time has elapsed between the readings for aging to have affected the elasticity of the rubber cuff and other rubber parts. Inability to increase the sensitivity of previous oscillometers when needed constitutes an additional important defect. It has not been uncommon in the past to observe no oscillation when attempting to measure segments of some limbs in which the appearance of vitality or actual palpable pulsations gave strong evidence that a certain minimum of circulation existed. The instruments previously developed solely for visual reading have, of course, no means of making a permanent record. Those developed for the purpose of obtaining permanent records have been difficult to read visually, since no provision is made for the maintenance of pressure at any one level for a period long enough to permit accurate reading. Errors due to friction of pen and paper writing, to the overthrust of comparatively heavy writing arms, etc., are also to be found in older recorders. The expense of construction of the latter machines has been considerable.

The apparatus and method described below permit a standardized permanent record of the systolic expansion of segments of limbs to be made on photographic paper. Visual reading, though not preferred, may be made without the difficulty of shifting the base line and without error introduced by parallax. Sensitivity may be varied when needed. A minimum of moving parts has considerably reduced the possibility of error. Recording is without friction, being accomplished by a shadow within a beam of light. The expense of attaching the apparatus to a standard electrocardiographic camera is but very slightly more than the cost of the average visually read oscillometer.*

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* As presently designed, apparatus and method is for use only with the Cambridge Simplitrol.

Method and Apparatus

Oscillometric readings are basically dependent upon the expansion of a segment of an extremity against a confined, encircling, mercury or aneroid manometer, inflating bulb, and valve remain attached, and the ordinary sphygmomanometer, thus, is utilized just as in measuring the blood pressure. Oscillometric

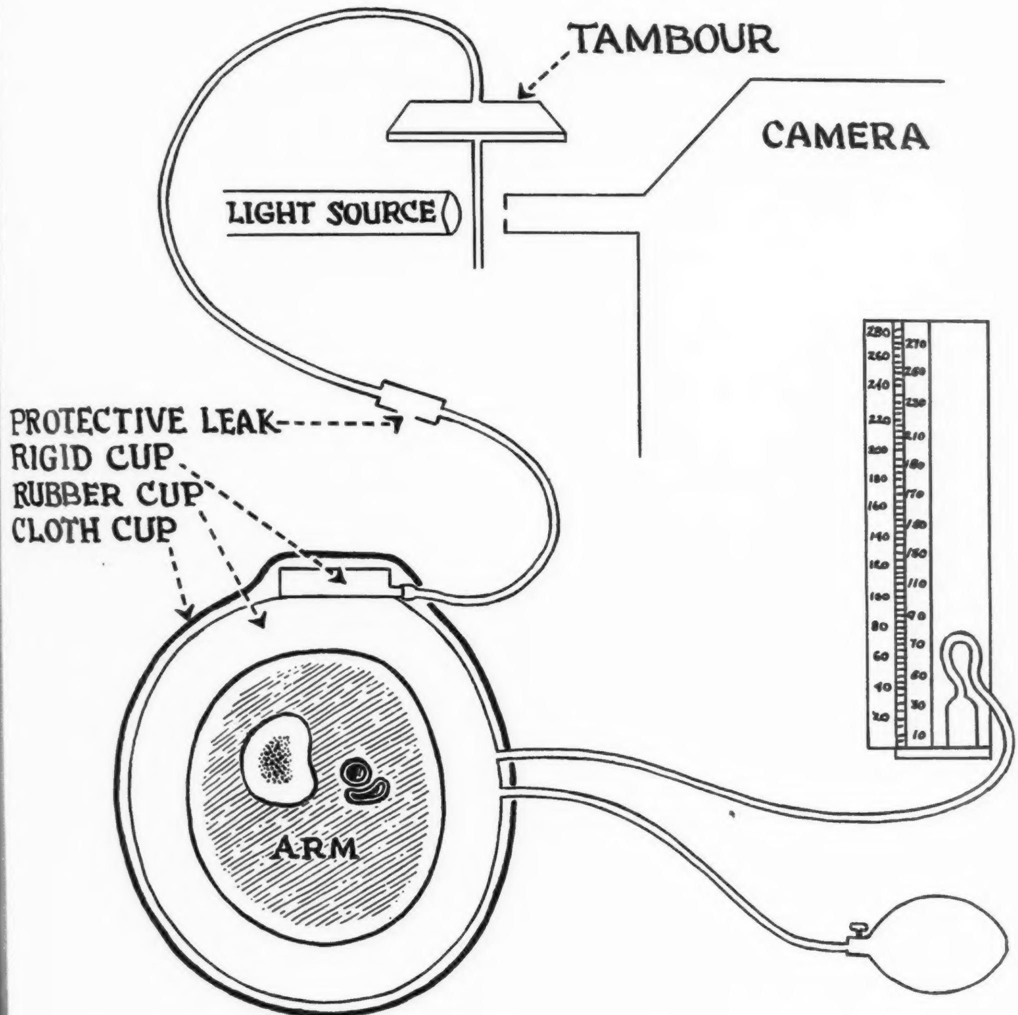

FIG. 1. Diagram of apparatus, showing cuff applied around arm. The location of the cup in relationship to the artery is not important for comparison readings.

inflated rubber cuff. Since the single rather than the double cuff is recommended for measurement of the oscillometric index,[1] the cloth-covered rubber bag of any sphygmomanometer is satisfactorily used. The measurements are made by amplifying and recording the pressure changes occurring within the rubber bag with each systolic inflow.

Pressure changes within the inflated rubber cuff are transmitted laterally to the walls of

the cuff. When one section of the outer wall of the rubber cuff lies snugly against the open portion of a stationary rigid cup, the interior, of which is maintained at atmospheric pressure, the expansion of this section is appreciable and quantitatively measureable for it forms a responsive diaphragm for the rigid cup. The concavity surrounding the periphery of the central cup, the other leads to the central cup itself.

The plastic cup is slipped between the cover cloth and the outer wall of the rubber bag of the sphygmomanometer arm piece so that the opening of the cup lies against the rubber and

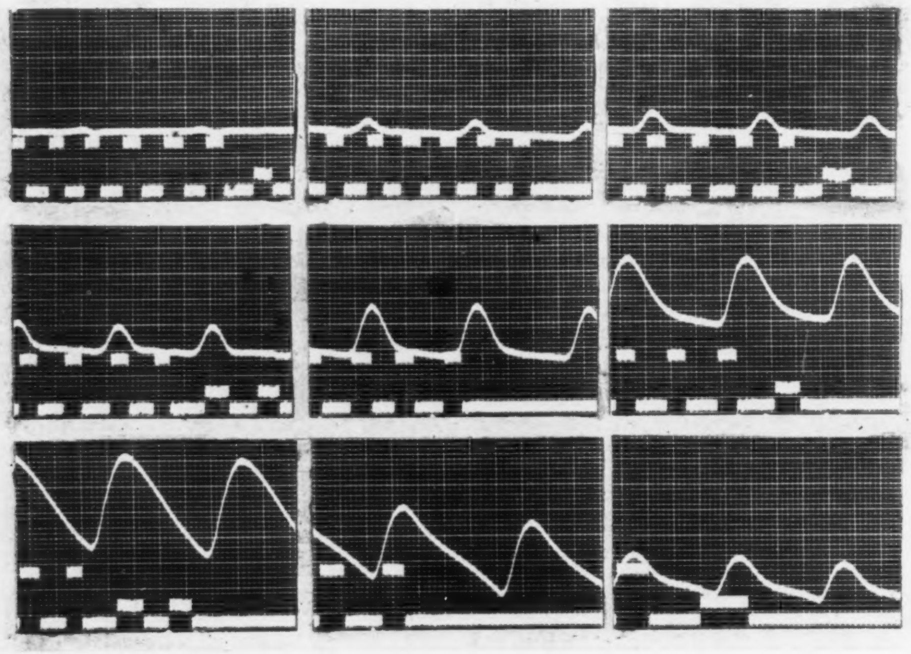

Fig. 2.—Oscillometric curve from left calf of normal subject. Deviations from lower base line indicate level of pressure at which reading was obtained. Each large deviation represents 30 mm. Hg., and each smaller one 10 mm. Hg. The curve starts at 200 mm. and in steps of 20 mm. drops to 40 mm. Oscillometric index is found at 80 mm. See text for standardization used in this and succeeding illustrations.

A curve obtained immediately afterward under the same conditions with a visual oscillometer gave the following readings: 200 mm.: 0.2; 180 mm.: 0.5; 160 mm.: 0.75; 140 mm.: 1.0; 120 mm.: 1.6; 100 mm.: 2.7; 80 mm.: 4.0; 60 mm.: 2.4; 40 mm.: 0.6

Shifting of the base line noted in several recordings indicates the presence of a minute leak in the limb piece-sphygmomanometer system.

cup is made of a light plastic in the shape of a disc, is approximately $1\frac{3}{4}$ inches in outside diameter with a height of $\frac{3}{8}$ inches. The open face of the cup is double ridged at the edges. The diameter of the larger central concavity of the cup is $1\frac{3}{16}$ inches. Two metal leads project from the cup. One of these affords access of air at atmospheric pressure to the small so that the metal lead from the major cavity of the cup barely projects through the opening in the cloth cuff through which the tubes to the rubber cuff enter. The limb piece of the oscillometer thus consists of a sphygmomanometer with a small segment of the rubber cuff acting as a diaphragm beating with each expansion within the cuff against

the atmospheric pressure of the recording system. Coarse adjustments in the sensitivity of the instrument may be made by varying the size of the plastic cup. Larger or smaller cups will increase or decrease the recorded oscillations, respectively.

A light rubber tube of convenient length leads from the metal outlet of the central cup to the recording system proper. Inserted into the rubber tube is a metal air vent which serves the purpose of maintaining the recording system at atmospheric pressure at all times, except when it is desired to transmit oscillatory pressure waves from the rubber cuff to the recording tambour. The vent is small enough to be completely closed with the finger tip for this purpose.

The recording tambour was originally described by Henny, Boone, and Chamberlain[3] for recording the carotid pulse simultaneously with the electrokymogram, and modified somewhat for ease in commercial manufacture by the engineers of the Cambridge Instrument Company. The tambour consists of a thin rubber diaphragm fastened to a plastic capsule. From one edge to the center of the diaphragm is cemented the base of a thin aluminum pointer. The pointer turned at right angles to the base projects away from but in the central axis of the diaphragm. When mounted on the electrocardiograph the pointer projects into the light beam and casts a shadow on the visible white scale and on the recording paper. Two brass screws are found on the supporting mechanism of the tambour. The first moves the entire tambour and its housing in or out of the light beam. The second, by rotating the rubber diaphragm permits rotation of the plane of movement of the pointer from one at right angles to the light beam to one that lies in the direction of the light beam. Thus the amplitude of motion of the shadow of the pointer varies

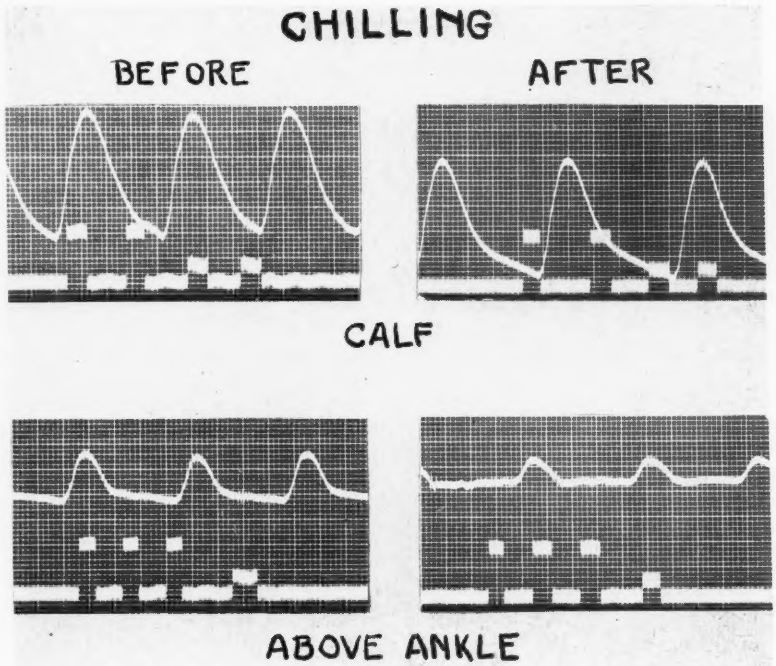

FIG. 3.—Tracings of right calf and lower leg above ankle taken immediately before and twenty minutes after removal of subject from high environmental temperature (84 F.; 29.0 C.) to air conditioned room (66 F.; 19.0 C). Oscillations were reduced 1.5 mm. in the calf tracing and 4.75 mm. in the lower leg. Only the oscillometric index is illustrated.

from its maximum to no excursion. Standardization of the instrument and adjustments of sensitivity for almost all clinical work may be made easily by rotation of the rubber diaphragm.

latory movements is comparatively simple, but recording by means of the electrocardiographic camera at normal speed is preferable. We have found it convenient to use the standardization current of the electrocardiographic

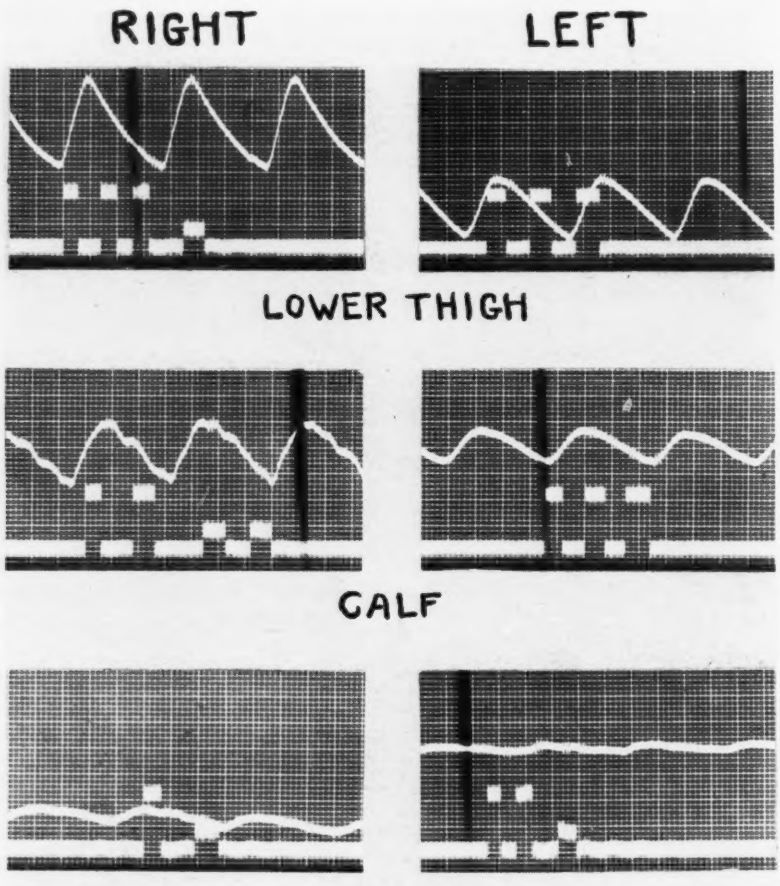

FIG. 4.—Subject with moderate symptoms of occlusive vascular disease in the left lower extremity. There is a difference in amplitude of oscillation amounting to 6 mm. in the lower thigh, 5 mm. at the calf, and 1.5 mm. at the foot when oscillometric indices here presented are compared.

Movements of the shadow of the pointer fall upon the white scale of the electrocardiograph. The phenomenon of parallax is therefore not involved, and if the entire system is without air leak, movements of the shadow are constant and without the shifting of the base line at each pressure measured. Reading of the oscil-

string to indicate the air pressure levels within the rubber cuff, using 3 millivolts for each 30 mm. increment of pressure as measured by the mercury manometer and 1 millivolt for each 10 mm. increment.

In order to obtain a standardized record, calibration is necessary prior to any recording.

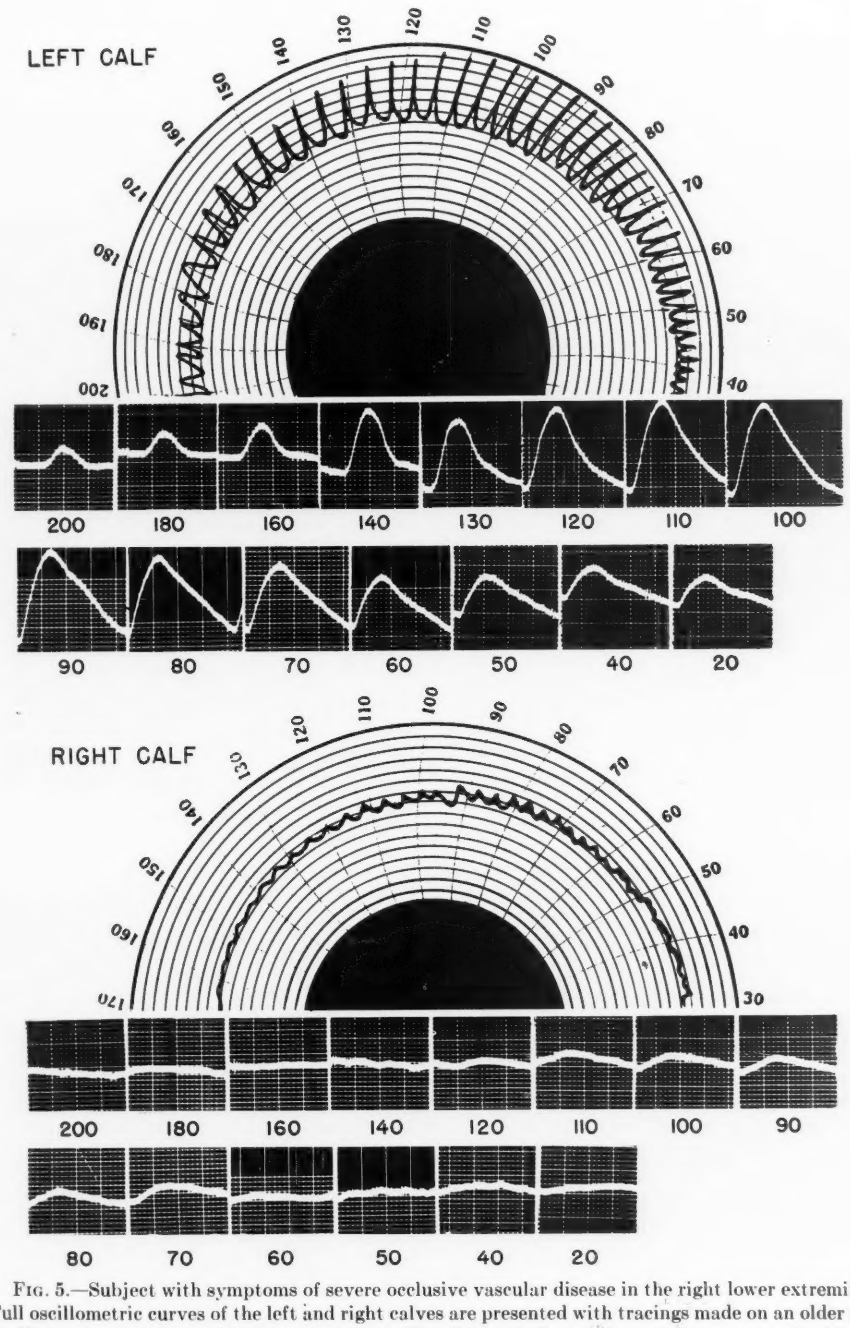

Fig. 5.—Subject with symptoms of severe occlusive vascular disease in the right lower extremity. Full oscillometric curves of the left and right calves are presented with tracings made on an older recording sphygmomanometer for comparison. The figures below each record represent the blood pressure in mm. Hg. at which the tracing was obtained. The curve is not a single tracing, each wave having been clipped from its own small recording.

Standardization may be accomplished by wrapping the sphygmomanometer cuff about a solid cylindrical object with a diameter of approximately $3\frac{1}{2}$ inches. The cuff is then inflated to a specified level, the air vent closed and the pressure dropped slowly in the cuff. During this procedure the shadow of the needle will move. Amplitude of shadow movement for any specified drop in pressure may then be adjusted as desired by rotation of the rubber diaphragm. Our early records (and those used in the illustrations) were made using a tambour not possessed of the rotating mechanism necessary for varying the amplitude of the string shadow. Sensitivity for this apparatus was thus constant. Using one particular sphygmomanometer it was found that a drop of 4 mm. of the mercury column from 110 mm. to 106 mm. occasioned a movement of the needle shadow of 25 millimeters. For the past eight months at the New York University Hospital Clinic we have had the newer type of tambour available and have standardized our records so that a drop of 10 mm., from 100 mm. to 90 mm., caused a shift in the needle shadow of exactly 10 millimeters. It is to be noted that this method of calibrating the entire system compensates for variance in the elasticity of different rubber cuffs and diaphragms, and for the aging processes of these rubber parts in the same apparatus. As pointed out above, if gross changes in sensitivity seem desirable for some special problem, the size of the plastic cup may be varied. We have not found this necessary up to this time.

Following calibration and notation of the standard used, a record is made by applying the cuff of the sphygmomanometer to the part of the extremity to be studied, the cuff inflated to a point above the local systolic pressure, the air vent closed with the tip of the finger and the movements of the needle shadow observed. A camera recording of the oscillations and markings, indicating the amount of air pressure in the cuff, should be made at this time. Upon completion of the recording of several waves, the air leak should be opened at once. The pressure in the cuff should then be dropped in increments equivalent to 10 mm. of mercury, and recordings taken of oscillations occurring at each new lower pressure. For purposes of economy we have occasionally made visual readings and then recorded the oscillations which appeared largest as well as those 10 mm. above and those 10 mm. below the maximum excursions. The records above and below the observed maximum constitute a check on the accuracy of visual observation since on measurement of the finished records both should be smaller than the oscillations chosen visually as the largest.

Clinical Use

The apparatus and method described have now been in use for approximately eight months in the peripheral vascular disease clinic at the New York University Hospital and for over two years in the private practice of one of us (J.A.O.). Studies have been made of the progress of vascular disease, of the effectiveness of vasodilating drugs and of sympathetic blocking procedures. The instrument has proved of particular value in determining the amount of spastic component present in the major arteries in various peripheral vascular diseases by taking records before and after vasodilating procedures and in determining the level of effective circulation following acute vascular occlusions.

These observations have made it obvious that the role of oscillometry in the study of peripheral vascular disease must be re-evaluated, using this new technic. Studies for this purpose are under way and will be reported subsequently.

Comment

In developing this technic for oscillometry we have attempted to overcome the defects which we feel have hitherto made oscillometry unsatisfactory. Shifting of the base line does not occur if the system is leak-tight. Parallax in visual observation does not exist since the observed oscillations are those of a shadow thrown directly onto a fixed scale. Oscillation may be observed for as long a period as seems

necessary for accuracy. There are no mechanical joints nor is there friction in the writing mechanism. Amplification is produced by the increased excursions of the tip of a rigid pointer swinging through an arc and the optical system of the electrocardiograph. Distortion and error in amplification are thus reduced to an inappreciable minimum. Standardized records are obtainable and it is possible to vary the sensitivity of the apparatus grossly by using smaller or larger segments of the rubber cuff as a diaphragm. Finer adjustments in sensitivity may be made by rotating the plane of movement of the pointer in its relation to the fixed beam of light.

Summary

1. A new technic for obtaining oscillometric measurements is described in detail.
2. Standardized records are obtainable.
3. Several sample records are exhibited.

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Vasomotor Reactions to Heat among Patients with Arterial Disease

By TRAVIS WINSOR, M.D.

Plethysmographic studies of the vasomotor reactions of the digits accompanying body heating were of value in the early detection of peripheral arterial disease. In normal individuals, labile vasomotor activity was shown by great changes in digital volume (a large pulse, alpha and beta waves). These changes were diminished or absent in patients with peripheral arterial disease.

IT HAS long been recognized that the response to body heating, as demonstrated through measurements of the resulting changes in the skin temperature of the extremities, permits a gross but useful estimate of the vasomotor reactions in patients with arterial disease.[1–8] In the meantime, the plethysmographic method has been considerably improved through the introduction of a portable appliance[9] as well as of a set of terms describing the characteristic wave forms in the plethysmogram.[10] Through application of this method it has now become possible to ascertain the finer details of the vasomotor responses to body heating as they become apparent in the digits of normal individuals as well as of patients with arterial disease. Thus, characteristic patterns can be distinguished, which may prove of considerable aid in the diagnosis of peripheral vascular disease.

Vasomotor reactions to body heating were studied in 20 normal individuals and 20 patients with arterial disease. The age of the normal individuals varied between 19 and 28 years, with an average of 21 years; 16 were men, four were women. Of the patients with arterial disease, 14 had arteriosclerosis obliterans, while 6 suffered from thromboangiitis obliterans; in ten instances, arterial disease had progressed to ulceration of heel, foot or digits.

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Experiments were conducted in a room with a temperature of 25 C. ± 1.5 degrees, the air velocity amounting ordinarily to less than 8 feet per minute, but at no time exceeding 12 feet per minute. In normal individuals, control tests were first carried out, following a rest period of sixty minutes' duration, with the subject lying on a horizontal bed, dressed in a hospital gown and covered with one light woolen blanket.

Body heating was accomplished by covering the individual with two woolen blankets, as well as two electric pads measuring 34 x 64 cm. One pad was placed horizontally across shoulders, arms and chest, and the other longitudinally upon the legs. The pads were applied warm and were inserted between the blankets, which were tucked snugly about the neck, while fingers and toes remained exposed.

The Cambridge pneumo-plethysmograph was employed,[9, 11] and the plethysmogram was standardized so that volume changes were obtained in cubic millimeters per 5 cc. of tissue per second. The amplitude of pulsations was recorded in cubic millimeters per 5 cc. of tissue.

A digital cup was fastened to the right or left second toe with a non-constricting sealing material.[12, 13] The blood flow of the digits was determined through venous occlusion.[13] The collecting cuff was placed at the wrist or ankle and in selected cases at finger or toe. Venous occlusion was ordinarily accomplished by quickly inflating the collecting cuff to a pressure of 60 mm. Hg. Lower pressures were employed in selected patients with arterial disease. Flow rates obtained with the collecting cuff at the

wrist or ankle are referred to as relative flow rates.

Waves of the Normal Plethysmogram

Ordinarily, at least five different types of waves can be recognized in the plethysmogram[10, 14]: pulse, respiration, alpha, beta and gamma waves (fig. 1).

The pulse wave represents changes in the digital volume, which are primarily influenced by cardiac output, caliber of arteries and arterioles, as well as tissue distensibility. Contour, frequency and amplitude of the pulse wave are often modified through arterial disease.[15–19] The contour of the pulse wave in the plethysmogram is not unlike that of the arterial pulse wave. The dicrotic notch can ordinarily be observed in the plethysmogram of normal individuals resting in a comfortable environment, and it becomes more prominent following body heating. In the plethysmogram of patients with advanced arterial obstruction, on the other hand, it is, as a rule, not possible to detect a dicrotic notch, even after body heating. The frequency of the wave is determined by the pulse rate. The amplitude of the pulse wave in the plethysmogram is constant only in the presence of extreme vasodilatation or vasoconstriction, but varies when the sympathetic tone is labile, as especially in normal individuals at ease in a comfortable environment. The amplitude is reduced under the influence of cold or pain, and by many emotional states, especially startle, fear, fright, anxiety, and probably embarrassment, as well as by certain mental processes, as for example simple multiplication. It is, on the other hand, increased through relaxation, contentment and sleep, and also by medication with nitroglycerin and prostigmine, as well as through general anesthesia and spinal and peripheral nerve block.[20]

The respiration wave is an expression of inconstant variations in the digital volume, dependent upon pulmonary activity.[21, 22] Inspiration ordinarily produces decrease of digital volume; expiration results in rise in systemic blood pressure and concomitant increase of digital volume.[23–26] Contour, frequency and amplitude of respiration waves depend not only on type and frequency of respiration but also on numerous other factors; the waves may, for instance, be small or entirely absent in patients with arterial disease, and become occasionally more conspicuous under the influence of body heating. Respiration waves are generally more pronounced in the fingers than in the toes, presumably because of higher vasomotor tone in the lower extremities.

The alpha, beta and gamma waves result in all probability from changes in vasomotor tone, and are of lower frequency than the other waves. These waves are often independent of variations in the blood pressure[27] and under carefully controlled conditions show a characteristic rhythmic pattern. Contour and amplitude of alpha, beta and gamma waves are subject to numerous influences: they are enlarged through contentment, sleep,[28] and mild body heating, but are reduced through anxiety or in patients suffering from certain types of arterial or tissue diseases. Alpha waves in the plethysmogram may or may not be accompanied by beta and gamma waves.[10] In addition to changes in vasomotor tone, gamma waves are dependent on shifts in tissue fluids[29, 30] and also on variations of the temperature in the immediate environment of the digit.

Influence of Body Heating on the Plethysmogram of Healthy and Diseased Individuals

The results of the previously outlined experiments lead to the conclusion that normal individuals, patients with moderate arterial disease without ulceration, and patients with advanced arterial disease with ulceration of the extremities show distinct differences in their respective vasomotor reactions toward body heating.

In the plethysmogram of a *normal* individual, application of damp towels to legs and trunk for a period of five minutes resulted in low pulse and alpha waves, while no respiration and beta waves could be observed (fig. 2, *A*). Clinically, the patient presented cool, white extremities with constricted veins, indicating a high grade of vasoconstriction as well as a markedly decreased rate of blood flow. When, after removal of the damp towels, the body was covered with a sheet, the pulse waves increased in amplitude

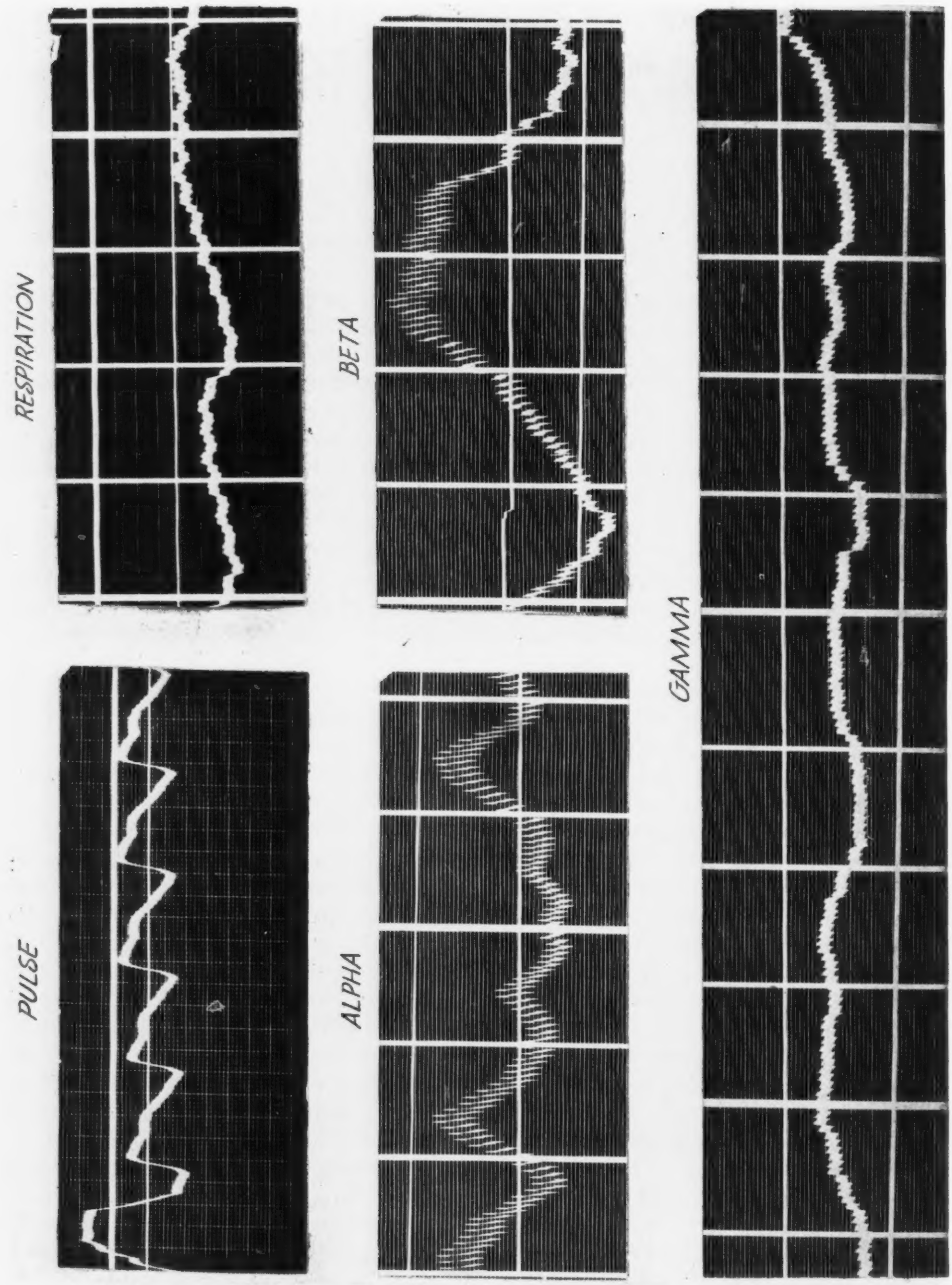

FIG. 1.—Five different types of waves can be recognized in the plethysmogram: pulse, respiration, alpha, beta and gamma waves, with a frequency of 65, 16, 5.5, 1, and 0.1 cycles per minute, respectively.

and beta waves became apparent (fig. 2, *B*). A tracing made ten minutes after the patient had been covered with a light woolen blanket and two electric pads were applied revealed pulse waves of variable amplitude and moderate size, as well as more prominent alpha and beta waves (fig. 2, *C*). Clinically, it was observed that the patient's skin was warmer and had a more pinkish appearance, due to increased blood flow and probably also to early release of vasomotor tone. A second blanket was added at this time, and after twenty-three minutes of body heating it was observed that the pulse waves were of variable amplitude, becoming larger with increasing digital volume, while the beta waves were regular and of high amplitude and frequency (fig. 2, *D*). Another plethysmogram made after heat had been applied for thirty minutes showed further increase in the amplitude of the pulse waves, particularly at the apices of the beta waves. The alpha waves were less prominent than in earlier tracings, while the beta waves showed lower frequency combined with high amplitude (fig. 2, *E*). After forty-five minutes of heat the amplitudes of the pulse waves were large and constant, but alpha and beta waves had become small (fig. 2, *F*). Clinically, the digits were hot, pink and damp, and with dilated veins, indicating a high degree of vasodilatation and little fluctuation in the vasomotor tone.

Whenever the wave pattern in serial plethysmographic tracings shows these typical changes it may be concluded that the arterial system is patent, the digital tissues possess normal distensibility, and the sympathetic nervous system is intact.

The relative toe flow, which after application of damp towels amounted to 4.0 cu. mm. per 5 cc. per second, rose progressively to reach a value of 33.0 cu. mm. per 5 cc. per second after forty-five minutes of body heating. This increase of blood flow to the toe is not only due to a decrease in peripheral resistance but probably also to greater cardiac output.

The mean, maximum, and minimum values for pulse, respiration, alpha and beta waves as well as the rates of blood flow to the toe obtained in tracings of twenty normal subjects at room temperature and during ten to forty minutes of body heating are presented in table 1.

The changes in the plethysmogram of patients with *moderate arterial disease without ulceration* of the extremities, brought about through body heating, show characteristic differences from the response of normal individuals. This fact becomes clearly apparent in the tracings of a 42 year old woman who was hospitalized because of backache, menorrhagia and intermittent claudication of four years' duration. After walking one quarter of a block, bilateral thigh and calf pains developed and the patient exhibited the "aortic waddle." An abdominal systolic murmur was recorded. Oscillometric readings above the knees were 0.5 unit, above the elbows 6.0 units. Blood pressure above the knees amounted to 90 mm. Hg, above the elbow to 140 mm. Hg. The diagnosis was arteriosclerosis obliterans of the abdominal aorta.

With the patient resting in a comfortable environment the pulse waves had an amplitude of 0.0 cu. mm., respiration waves were absent, alpha waves insignificant, while beta waves with an amplitude of 8.0 cu. mm. occurred at a frequency of one cycle per minute. The relative blood flow to the toe was 1.5 cu. mm. per 5 cc. per second, (fig. 3, *A*). Following application of heat to the body for thirty-five minutes, the pulse wave increased to 0.5 cu. mm., respiration waves occasionally became visible, and alpha waves showed amplitudes of 4.0 cu. mm. with a frequency of 6 per minute, while the amplitude of beta waves measured approximately 15.0 cu. mm. with a frequency of 0.9 cycle per minute. Relative blood flow to the toe had increased to 6.8 cu. mm. per 5 cc. per second (fig. 3, *B*).

The findings in this case are typical of the plethysmogram of patients with moderate arterial disease in which the contour of the pulse wave is often rounded, especially following application of heat, and the dicrotic notch remains indistinct. While thus a moderate lack of vasomotor response becomes apparent, a sufficient degree of vasomotor activity is still encountered in patients of this type to suggest that benefit may be expected from medical treatment or sympathectomy. Subcutaneous injection of prostigmine, 1:1000, was carried out in 5 of a

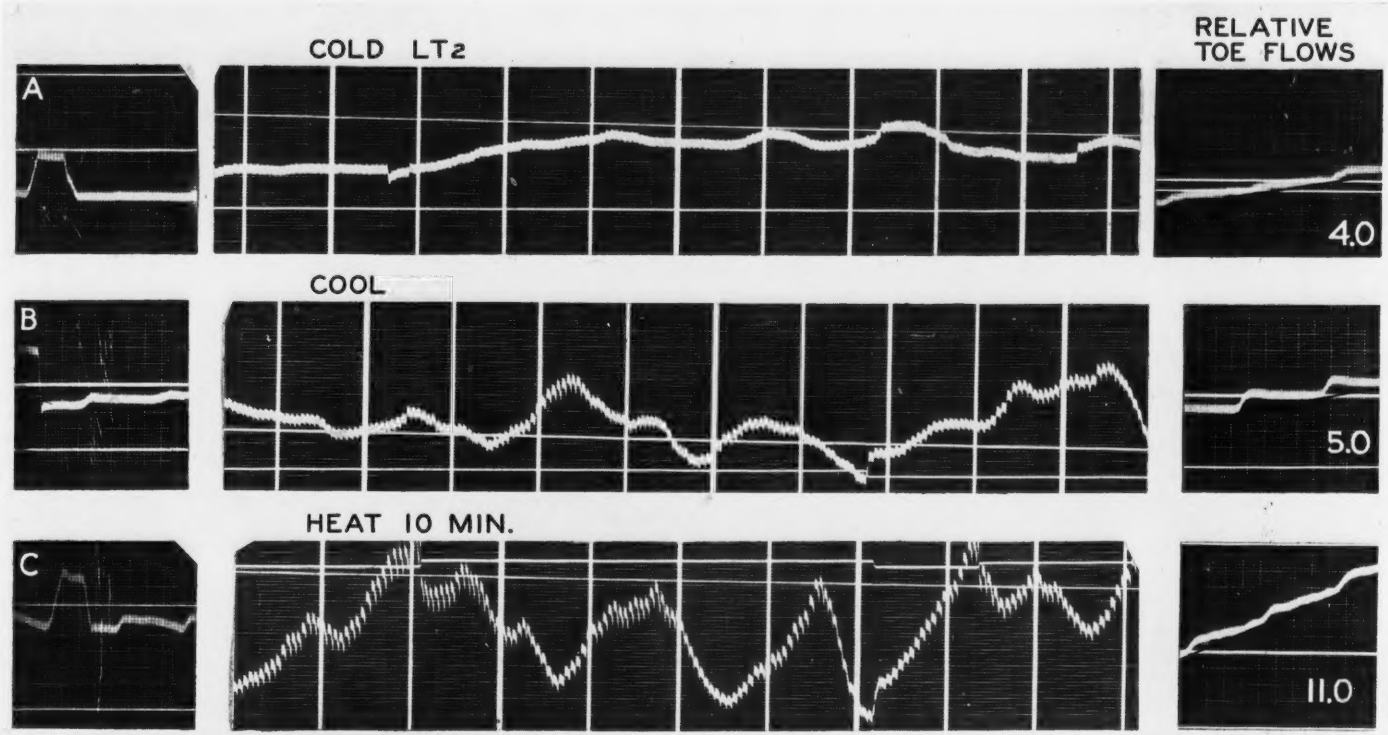

FIG. 2.—Effect of body cooling and body heating on the wave pattern of the plethysmogram in a normal 25 year old man. Body cooling (*A*) resulted in lowered pulse and alpha waves, indicating marked vasoconstriction. Intense body heating (*F*) (next page) resulted in pulse waves of high amplitude accompanied by small alpha and beta waves, indicating a high degree of vasodilatation. Intermediate degrees of body heating (*B*, *C*, *D*, *E*) resulted in pulse waves of variable amplitudes and large alpha and beta waves.

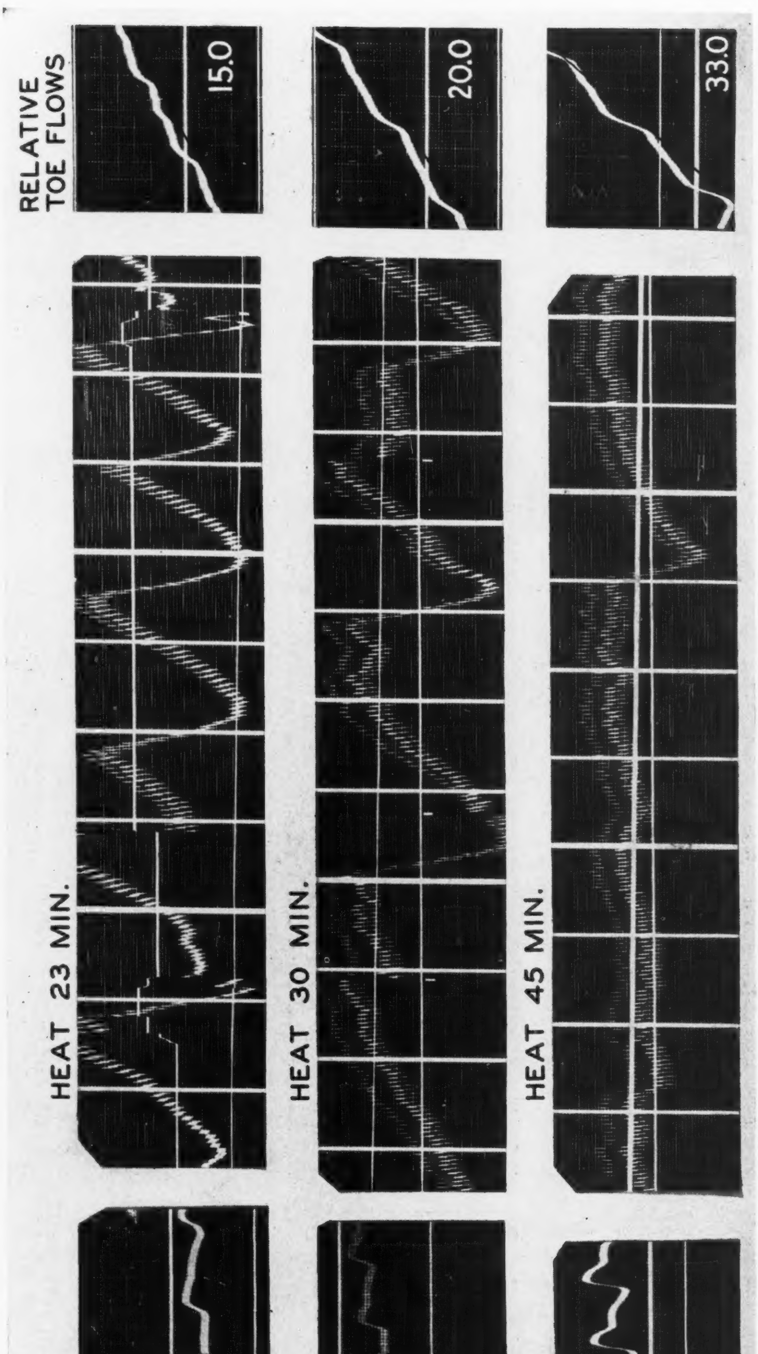
RELATIVE TOE FLOWS
15.0
20.0
33.0
HEAT 23 MIN.
HEAT 30 MIN.
HEAT 45 MIN.
D
E
F

FIG. 2.—Cont'd

TABLE 1.—*Mean, maximum and minimum values for pulse, respiration, alpha and beta waves as well as rates of blood flow to the toe obtained in twenty normal subjects, at room temperature and during body heating, for varying periods of time*

	Pulse Waves (Cu.mm.)					*Respiration Waves† (Cu.mm.)*			*Alpha Waves*					*Beta Waves*						*Blood Flow (Cu.mm. per 5 cc. per sec.)*				
	Minutes*								Minutes					Minutes						Minutes				
	0	10	20	30	40	Cool	Warm		0	10	20	30	40	0	10	20	30	40		0	10	20	30	40
Mean	6.2	8.5	12.3	13.8	15.6	—	1.1	Cycles per min.	6.0	6.0	6.7	5.5	5.5	1.0	1.7	1.5	1.3	1.4	Ankle Cuff	7.6	21.5	20.4	30.1	—
								Cu. mm.	4.0	9.0	6.0	5.0	1.5	11.0	18.0	20.0	30.0	35.0	Toe Cuff	17.4	34.1	50.7	59.6	49.9
Max.	13.0	18.2	15.6	18.2	16.5	—	2.0	Cycles per min.	4.0	4.0	5.0	4.0	4.0	0.7	1.0	1.2	1.0	1.3	Ankle Cuff	27.3	42.0	40.0	70.0	—
								Cu. mm.	15.0	20.0	8.0	15.0	2.0	20.0	30.0	40.0	50.0	50.0	Toe Cuff	32.4	40.8	59.2	77.0	60.0
Min.	0.6	1.1	2.2	8.8	12.6	—	0.5	Cycles per min.	10.0	7.5	8.6	10.0	6.7	3.0	4.0	2.4	2.0	1.5	Ankle Cuff	1.0	8.5	11.7	14.0	—
								Cu. mm.	1.0	4.0	3.0	2.0	1.0	2.0	10.0	10.0	12.0	20.0	Toe Cuff	7.0	27.5	33.8	41.4	39.7

* Duration of body heating.
† Respiration waves appeared in only 8 subjects.

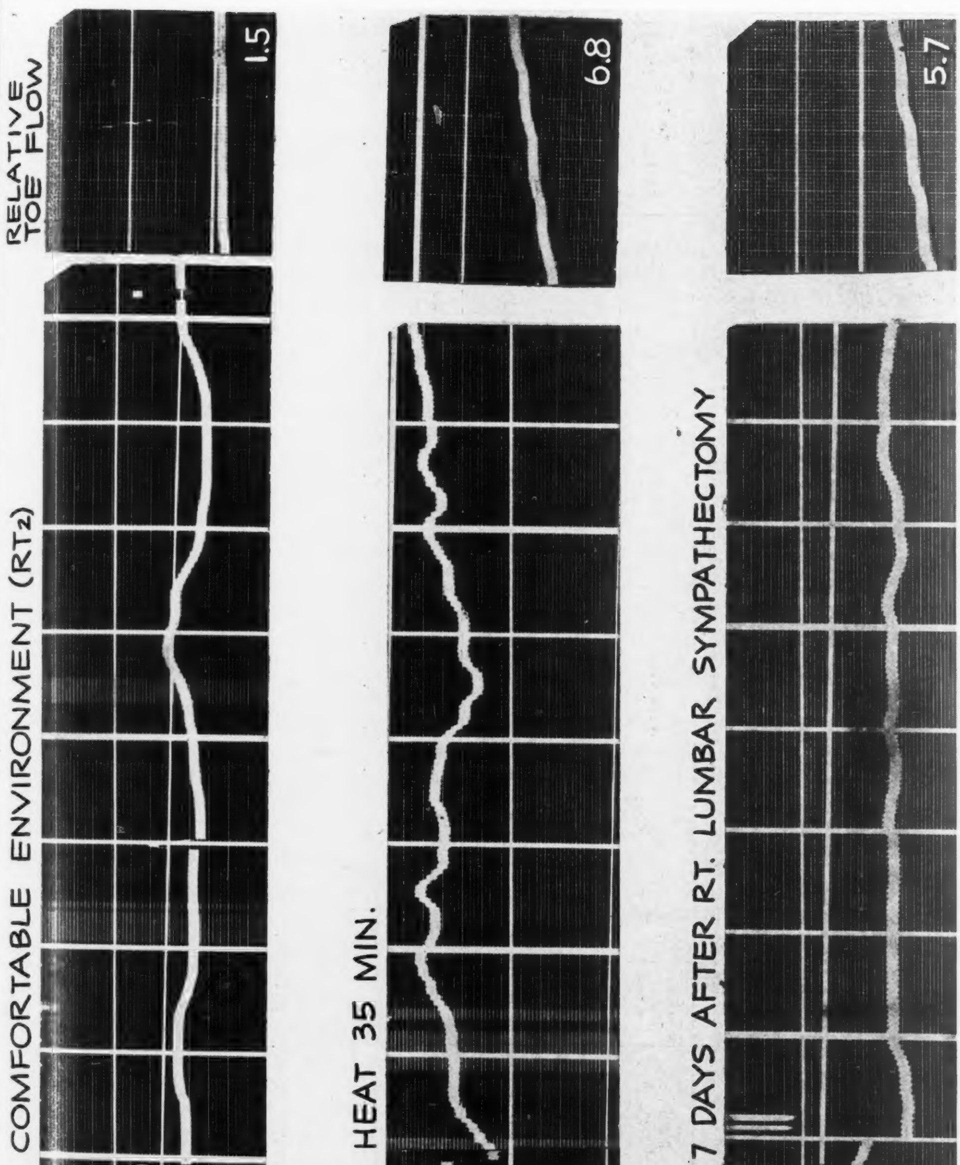

FIG. 3.—Effect of body heating on the wave pattern of the plethysmogram in a patient with moderate arterial disease without ulceration of the extremities. Body heating (*B*) resulted in the appearance of pulse, alpha and beta waves, suggesting a fair degree of vasomotor activity. The relative blood-flow to the toe increased moderately to a value of 6.8 cu. mm. per 5 cc. per second, as compared with a normal of 30.0 cu. mm. This patient derived subjective and objective benefit from sympathectomy.

TABLE 2.—*Mean, maximum and minimum values for pulse, respiration, alpha and beta waves as well as rates of blood flow to the toe obtained in ten patients with moderate arterial disease without ulceration of the extremities, at room temperature and during body heating for varying periods of time*

	Pulse Waves (Cu.mm.)					*Respiration Waves† (Cu.mm.)*			*Alpha Waves*					*Beta Waves*						*Blood Flow (Cu.mm. per 5 cc. per sec.)*				
	Minutes*								Minutes					Minutes						Minutes				
	0	10	20	30	40	Cool	Warm		0	10	20	30	40	0	10	20	30	40		0	10	20	30	40
Mean	0.8	0.8	1.3	0.8	—	—	1.4	Cycles per min.	7.5	6.0	5.5	5.0	8.6	1.4	1.4	1.3	1.3	8.4	Ankle Cuff	3.4	7.1	7.8	8.3	7.8
								Cu. mm.	4.0	5.0	3.0	3.9	3.0	5.5	3.7	8.8	8.8	8.4	Toe Cuff	10.5	—	—	18.5	17.6
Max.	4.0	1.2	2.8	1.2	—	—	2.0	Cycles per min.	5.5	4.3	3.8	4.0	6.7	0.8	1.3	1.2	1.0	0.8	Ankle Cuff	8.0	9.8	9.9	11.0	14.0
								Cu. mm.	7.0	6.0	5.0	8.0	8.0	15.0	5.0	15.0	15.0	25.0	Toe Cuff	24.2	—	—	39.9	31.5
Min.	0.1	0.3	0.6	0.4	—	—	0.5	Cycles per min.	10.0	8.6	7.5	7.5	10.0	10.0	1.4	1.6	2.0	4.0	Ankle Cuff	0.6	4.2	3.5	3.5	1.0
								Cu. mm.	2.0	2.0	1.0	0.5	2.0	2.0	3.0	5.0	3.0	2.0	Toe Cuff	2.5	—	—	7.2	3.6

* Duration of body heating.

† Respiration waves appeared in only 3 patients.

series of 10 patients with moderate arterial disease, and produced amplitudes of the pulse waves three times as large as those observed prior to medication, with the patient resting in a comfortable environment. Lumbar sympathetic block in 10 patients, spinal anesthesia in 4 patients, as well as lumbar sympathectomy in 5 patients resulted in an increase of the amplitudes of the pulse waves to four times the value of earlier readings with the patient in a comfortable environment, and also caused almost complete disappearance of alpha and beta waves. At the same time, the rate of blood flow to the toe increased three to eight times.

In the case mentioned above, right sympathectomy was advised. At time of operation the aorta was found to be small and firm, and an aortic thrill was detected. Seven days postoperatively the plethysmogram showed pulse waves with amplitudes of 0.6 cu. mm., alpha and beta waves were insignificantly small, and blood flow to the toe amounted to 5.7 cu. mm. per 5 cc. per second (fig. 3, *C*). Skin temperatures had increased 9 degrees C., and systolic blood pressure of the ankles was 10.0 mm. Hg. higher than preoperatively. Following uneventful recovery the patient was able to walk eight blocks without pain, and unquestionably sympathectomy proved to be of subjective as well as objective benefit.

The mean, maximum, and minimum values for pulse, respiration, alpha and beta waves as well as the rates of blood flow to the toe, obtained in tracings of 10 patients with moderate arterial disease without ulceration of the extremities observed at room temperature and during ten to forty minutes of body heating, are presented in table 2.

In the plethysmogram of individuals with *advanced arterial disease with ulceration* of the extremities, only small changes can be observed following application of heat to the body, as evident in the tracings of a 73 year old woman. A small ulcer appeared on the dorsum of the left fourth toe and she complained of pain in both legs on walking 50 steps. Systolic blood pressure of feet, ankles, calves and thighs was distinctly lower than in hand, wrist, antebrachium and brachium. The diagnosis was arteriosclerosis obliterans of the abdominal aorta and popliteal artery.

When the patient was resting in a comfortable environment, no pulse, respiration, alpha or beta waves appeared in the plethysmogram (fig. 4, *A*). After fifteen minutes of body heating, beta waves not exceeding 5 cu. mm. could be observed (fig. 4, *B*), but they were much less prominent, attaining not even to 2.0 cu. mm., when heat was applied for a period of thirty minutes (fig. 4, *C*). At the same time the relative rate of blood flow to the toe, which had increased from 0.1 cu. mm. per 5 cc. per second at room temperature to 1.1 cu. mm. per 5 cc. per second following fifteen minutes of body heating, again declined after thirty minutes to 0.1 cu. mm. per 5 cc. per second. This effect is probably due to vasodilatation of normal vessels elsewhere in the body, causing the blood to be shunted away from the diseased extremity.[31]

Observations in a group of 10 patients with advanced arterial disease with ulceration of the extremities showed that evidence of vasomotor activity following body heating was almost completely lacking in the plethysmogram. This finding, together with a minimal increase in the relative blood flow to the toe, is indicative of severe organic arterial disease, while hardly any vasospasm is present, and only little collateral circulation available. It is therefore not surprising to find that 5 patients treated with subcutaneous injections of prostigmine, 1:1000, showed no peripheral vascular response. Intravenous injection of tetraethylammonium chloride, 500 mg., also failed to produce any changes in the plethysmographic pattern. Lumbar sympathectomy performed in 5 patients was not followed by any definite changes in the plethysmogram or by increased blood flow to the toe. This negligible benefit of surgery is clearly demonstrated in the case mentioned above (fig. 4, *D*). No significant postoperative improvement was observed in any of these patients.

The mean, maximum, and minimum values for pulse, respiration, alpha and beta waves as well as the rates of blood flow to the toe, obtained in tracings of 10 patients with moder-

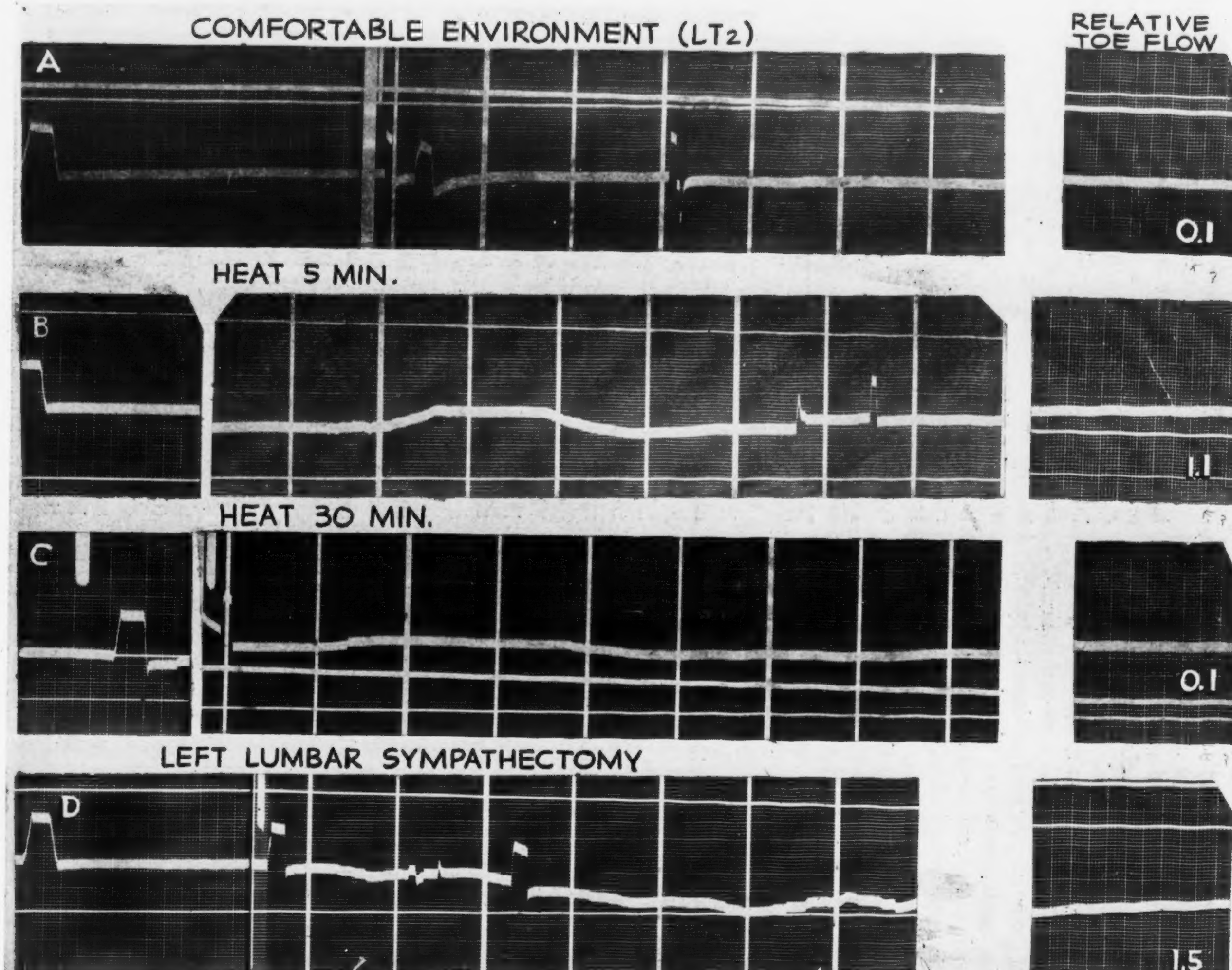

FIG. 4.—Effect of body heating on the wave pattern of the plethysmogram in a patient with advanced arterial disease, with ulceration of the extremities. Body heating (*B*) resulted in the appearance of low beta waves. The relative toe flow increased slightly with mild body heating, but decreased with prolonged application of heat (*C*). This patient was not materially benefited by lumbar sympathectomy

TABLE 3.—*Mean, maximum and minimum values for pulse, respiration, alpha and beta waves as well as rates of blood flow to the toe obtained in ten patients with advanced arterial disease with ulceration of the extremities at room temperature and during body heating for varying periods of time*

	Pulse Wave (Cu.mm.)					Respiration Waves (Cu.mm.)			Alpha Waves†					Beta Waves						Blood Flow (Cu.mm. per 5 per sec.)				
	Minutes*								Minutes					Minutes						Minutes				
	0	10	20	30	40	Cool	Warm		0	10	20	30	40	0	10	20	30	40		0	10	20	30	40
Mean	0.4	0.2	—	0.2	1.1	—	—	Cycles per min.	—	—	—	6.0	—	1.3	1.5	1.4	1.5	—	Ankle Cuff	2.9	4.7	4.9	4.3	3.9
								Cu. mm.	—	—	—	0.1	—	2.3	2.3	3.0	3.7	—	Toe Cuff	—	—	—	—	—
Max.	1.5	0.3	—	0.3	3.6	—	—	Cycles per min.	—	—	—	—	—	1.0	1.0	1.3	1.0	—	Ankle Cuff	8.4	7.0	7.2	8.4	7.8
								Cu. mm.	—	—	—	—	—	3.0	4.0	5.0	5.0	—	Toe Cuff	—	—	—	—	—
Min.	0.1	0.1	—	0.1	0.1	—	—	Cycles per min.	—	—	—	—	—	2.0	3.0	1.5	2.0	—	Ankle Cuff	0.1	2.3	0.7	0.1	0.1
								Cu. mm.	—	—	—	—	—	2.0	1.0	1.0	2.0	—	Toe Cuff	—	—	—	—	—

* Duration of body heating.
† Appeared in only one patient.

ate arterial disease with ulceration of the extremities observed at room temperature and during ten to forty minutes of body heating, are presented in table 3.

A comparison of the submitted data shows that the vasomotor changes following body heating produce characteristic differences in the plethysmographic wave pattern. Plethysmographic tracings are, therefore, of great aid in evaluating the degree of arterial disease present, as well as in deciding on a course of therapy.

Summary

The pneumo-plethysmograph was employed to study the vasomotor response to body heating in three groups of subjects: normal individuals, patients with moderate arterial disease without ulceration of the extremities, and patients with advanced arterial disease with ulceration of the extremities. The changes in the plethysmogram of normal individuals, occurring after body heating for varying periods of time, indicate the presence of marked vasomotor activity. Tracings of individuals with moderate arterial disease show, under the influence of body heating, wave forms of lower amplitudes, while in the presence of advanced arterial disease only marginal changes occur in the plethysmographic wave pattern. From these findings it can be deduced that in moderate arterial disease a diminished degree of vasomotor activity remains, yet sufficiently great to make medical treatment or sympathectomy advisable. In advanced arterial disease, on the other hand, vasomotor activity is almost completely absent, and no substantial benefit can be expected from either form of treatment.

Plethysmographic tracings can be of great aid in planning the most promising course of therapy in peripheral vascular disease.

Acknowledgments

Gratitude is expressed to Dr. B. O. Raulston for the encouragement and cooperation extended during the course of this research. The valuable technical assistance of Grayce S. Fleming is sincerely acknowledged.

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Erythromelalgia Treated with Posterior Pituitary Extract: Report of a Case

By M. Hill Metz, M.D.

Erythromelalgia is a rare vasomotor neurosis of the extremities, with no accepted form of treatment. Posterior pituitary desiccated powder administered by nasal insufflation has a vasoconstricting action lasting for eight to twelve hours. With the use of this agent, one patient was protected from the incapacitating symptoms of erythromelalgia during the summer months.

ERYTHROMELALGIA is a rare vasomotor neurosis of the extremities. The symptoms of this disease occur in the hands but are more often seen in the feet. These symptoms are redness and pain which are increased by warmth, by exercise, and by the dependent positions of the limbs. At first the distress is noticed in the heat of summer but in time it may extend into the winter months also. The pain is burning in character and is aggravated by walking, standing, and by the covering of bedclothes.

The skin of the involved part will appear very pink and will be very sensitive and tender to any pressure. There are always normal arterial pulsations throughout the feet even when the pain is accentuated. The temperature of the skin is elevated and raising the foot above the heart level will lessen the burning sensation and the flush somewhat, but it will not produce blanching of the skin as seen in other peripheral vascular diseases. Cool applications also quiet the discomfort. Some of the above symptoms are seen in association with other vascular diseases especially thromboangiitis obliterans and arteriosclerosis, but the patient here reported showed no evidence of these diseases.

Telford and Simmons[1] commented on the infrequency of this disorder and reported excellent results in 3 cases following lumbar-sympathetic ganglionectomy. They were of the opinion that the good results elucidated somewhat the nature of this disease. Smith and Allen[2] recommend 10 grains of acetylsalicylic acid several times daily for the relief of symptoms. Munson[3] reported some improvement when epinephrine was administered either by injection or inhalation.

Case Report

The patient, a 53 year old white man, first noticed burning pain and a pink color of his feet for short periods during the warmest days of the summer of 1947. There was no discomfort during the following winter months. He was first interviewed on May 15, 1948, at which time he complained of an intense burning and increased warmth of both feet particularly of the plantar surfaces. The distress was interfering with his occupation as a contractor because he was unable to stand during the latter part of the day. There was improvement in the evening after a few hours in bed but not complete relief. He had learned to bathe his feet in cool water for quick relief. There were no significant former illnesses other than six months of nervous exhaustion fifteen years previously. He had noticed the symptoms to be increased, and it was necessary for him to stop work sooner, on days when tension and frustration were apparent. Complete physical examination and routine laboratory tests revealed no abnormality. The skin of both feet was very red and there was moderate perspiration. The pain was increased by palpation and stroking. The arteries pulsated normally everywhere and were not significantly thickened.

It seemed reasonable to search for some drug or agent which would produce mild but prolonged constriction of the small blood vessels. Much experience had been accumulated in the use of posterior pituitary extract in the treatment of peptic ulcer,[4] and it was felt that this hormone might be the best substance available for controlling the abnormal vasodilation. It was already known that this extract had a prolonged action when administered by nasal insufflation, and the studies of Wolf and Wolff[5] on human subjects with gastric fistulas had demonstrated its action to last for eight to twelve hours. The duration of vasoconstriction could thereby be clearly observed.

This patient was instructed in the use of $\frac{3}{4}$ grain

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of posterior pituitary desiccated powder taken by nasal insufflation after breakfast and at 5 P.M. daily. There was distinct improvement after four days' treatment and then he was advised to take the powder three times daily. He remained free of incapacitating symptoms and there was a definite diminution of the red color of the skin. On August 15 the treatment was discontinued. In three days the pain had returned to such an extent that he could work only a half day. Treatment was again started and again there was control of the skin temperature and discomfort. After October 1, $\frac{1}{3}$ grain of the powder taken twice daily was sufficient, and by November 1 the daily temperature was such that treatment was discontinued. Only at infrequent intervals has the patient been annoyed during the winter months. Obviously no definite conclusions can be had from the result in one case of erythromelalgia but it is hoped that this therapeutic suggestion will be pursued further in vascular clinics where a large number of cases of this rare condition is seen.

Summary

The previously incapacitating symptoms of erythromelalgia were mild during the summer months for a patient who used posterior pituitary desiccated powder by nasal insufflation. This therapeutic approach is offered as a suggestion only, but it is hoped that those physicians who interest themselves in peripheral vascular disease will see fit to give it further trial.

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The Clinical Effect of Dihydroergocornine Methanesulphonate (DHO-180)* in Arterial Hypertension: A Preliminary Report

By R. M. Tandowsky, M.D.

A controlled clinical and statistical study of 47 unselected patients with sustained arterial hypertension who received dihydroergocornine intravenously and orally is presented. The study demonstrates the central effect of this drug in temporarily lowering the systolic and diastolic blood pressure and pulse rate. This action occurs irrespective of associated pathology or extent of the hypertensive state when the drug is given parenterally. Orally, little effect was demonstrated.

With the advent of surgical palliation,[1] interest has been renewed in the relationship of the sympathetic nervous system to arterial hypertension. This method of approach has often failed because it does not utilize all of the physiologic components which take part in this syndrome. The neurogenic control of the hypertensive state must include complete interruption of central and peripheral pressor impulses, with analogous activation of the depressors, and an inhibitory effect on the heart rate through the vagus. Earlier investigators[2–4] felt that this effect could be accomplished by a chemical agent. Due to the necessity for induced narcosis in animals then under experimental study, the central effect of depressor drugs proved worthless. Investigation[5, 6] demonstrated, however, both a peripheral and central rise of arterial blood pressure following the use of various ergot components, and this could be abolished by spinal cord section.[7] In a few instances ergot derivatives produced a fall in blood pressure,[8] and this fall was found to be due to inhibition of adrenergic function.[9] These studies suggested the presence of sympatholytic components in ergot.

During 1943 the various alkaloids of ergot were isolated[10] and of these ergotoxine was shown to consist of three alkaloid components: ergocrystine, ergocornine, and ergocryptine. Known polypeptides, they could be reduced by hydrolysis to lysergic acid, ammonia, one keto acid, and two varying amino acids. By further hydrogenation of the readily reducible double bond of lysergic acid, four distinct derivatives were isolated from the ergot alkaloids: dihydroergotomine, dihydroergocrystine, dihydroergocornine, and dihydroergocryptine. This reduced their toxicity and produced an appreciable sympatholytic effect not seen in their predecessors.[11] One of these alkaloids, dihydroergocornine, possesses a pure sympatholytic effect on the peripheral blood vessels of man.[12] The reduction of arterial blood pressure by the chemical means now in common use is mainly accomplished by direct peripheral action. This effect is often transitory and leads to objectionable manifestations because sympatholytic coordination of the higher centers is lacking. Compensatory acceleration of the heart rate results. Coordination of the sympatholytic and vagus centers appears to have a sound physiologic and pharmacologic basis in the control of the hypertensive state.

In this preliminary study we hope to show the usefulness of dihydroergocornine in sustained arterial hypertension. Being purely sympatholytic, this derivative has low toxicity and small therapeutic dosage. As a central vasodilator we feel that it may prove of value in distinguishing arterial hypertension of central ori-

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* Material for this study furnished by the Sandoz Chemical Works.

gin from the more complicated types of this disease seen clinically. Because this central effect does not produce sedation or narcosis, it may prove of value in the palliative treatment of arterial hypertension, particularly of central origin. It may also prove of value in the selection of those amenable to surgical relief and it may assist in the estimation of postoperative response. The following procedure and clinical data are presented to support some of these contentions.

Method of Study

The patients with hypertension utilized for this study were either hospitalized and mildly sedated for a period of not less than five days or constituted an ambulatory group under observation for a period of three months or more. All were placed on low sodium diets. A complete historical and clinical survey was made prior to selection for study. Those selected retained a basal systolic and diastolic blood pressure level above normal throughout the entire period of preliminary observation. Prior to the intravenous use of dihydroergocornine, blood pressure and pulse determinations were made at fifteen-minute intervals for a period of not less than sixty minutes. Both the mercury manometer and the Tycos recording sphygmomanometer were used to provide a double check. Unusual emotional factors were allayed by mild sedation. One group of 12 subjects received control therapy in the form of distilled water, normal saline, or glucose intravenously under the guise of specific therapy for their hypertension. The entire group then were given well diluted dihydroergocornine intravenously in dosage varying from 0.25 mg. to 0.5 milligram. Blood pressure and pulse determinations were recorded at fifteen minute intervals for a period of two hours and were obtained at intervals thereafter for twenty-four hours. When possible, this procedure was repeated on successive days, the dose being varied for the determination of cumulative effect. Biochemical, clinical observation, and electrocardiographic studies were made prior to and after this medication; then each patient was placed on the same drug orally in doses varying from 0.75 to 24 mg. daily. Those on oral medication were presumed to be ambulatory and were seen twice weekly. On each visit, prior to examination, they were required to rest in a supine position for a period of thirty minutes.

Material

The salient characteristics of the 47 patients receiving DHO-180 intravenously are recorded in table 1, where the individuals are arranged primarily according to the presence of congestive heart failure and cardiac hypertrophy and secondarily according to their diastolic pressures recorded just before the administration of the drug. It will be seen from the data cited in the table, that the group included a great diversity of blood pressures and pulse rates, a broad range of ages, both sexes, and a considerable variety and degree of cardiovascular and renal impairment. Two of the group had submitted to unsuccessful paravertebral sympathectomy within one year of this study. We felt that all had sustained arterial hypertension which varied little psychosomatically and was affected little by the methods of treatment now in common use.

Clinical Effects

The 12 patients utilized for the control study received their injections with the same technic and clinical follow-up as those receiving dihydroergocornine. No perceptible alterations in blood pressure or pulse rates were observed. These patients subsequently received dihydroergocornine.

The effects of dihydroergocornine given intravenously in a single dose (in amounts indicated in table 1) were generally a reduction of the systolic and diastolic blood pressure and slowing of the pulse. Only in the aged and in a few patients with extreme renal damage was this effect so small as to be inconsequential.

Detailed studies of the results obtained showed that the percentage reduction of the systolic pressure, diastolic pressure, and pulse rate was essentially identical in each patient of this series. Thus, if the systolic pressure fell to 80 per cent of the pretest reading, so also did the diastolic pressure and pulse rate; if one was unaffected so were the other two. In each time interval for two hours following medication these three measurements tended to change simultaneously and equally, provided they were each expressed as a percentage of the pretest level. After twenty-four hours, however, the diastolic pressure had generally returned to the untreated level while the systolic pressure and pulse rate remained slightly reduced. Because of this mode of action it was decided to present the findings in terms of percentages rather than in millimeters of mercury or beats per minute. The systolic pressure at each interval following the injection of dihydroergocornine was therefore expressed as a percentage of the pretest reading and the mean and standard deviation of these percentages for the 47 patients in this series were calculated at each time interval. The

TABLE 1.—*Chief Clinical Characteristics of Forty-seven Patients Treated with Dihydroergocornine Methanesulphonate (DHO-180) Intravenously*

# of Case	Age	Sex	Duration in Years	Pre-test Blood Pressure and Pulse	Major Findings	Concomitant Conditions	DHO-180 Dose (mg.)
1	49	F	5	220/124, 70	CF, CH, LAD, AR	Obesity	.5
2*	74	M	12	190/120, 92	CF, LAD, H (r.CVA), HR	Peptic Ulcer	.5
3*	47	M	4	158/110, 84	CF, CH, LAD, HR	Alcoholism	.5
4	64	M	6	194/104, 78	CF, LAD, H, IB, uremia	Syphilis	.5
5*	78	M	10	170/100, 84	CF, CH, AF,HR, MRD		.5
6	56	F	2	194/ 98, 72	CF, CH, LAD, SA, HR	Obesity, hot flashes	.35
7	51	M	4	208/ 78, 88	CF, LAD, HR, MRD	Obesity	.4
8*	64	M	10	160/ 70, 76	CF, CH, LAD, AR		.5
9	84	M	10	185/ 70, 88	CF, CH, LAD, AF, GAS, AR	Paget's Disease	.5
10	35	F	3	215/138, 89	sl. CF, LAD, RAsp, PS 2 yr.		.4
11	70	M	6	170/ 70, 82	sl. CF, LAD, HR		.5
12	52	F	3	190/110, 86	CF, AR, MRD	Arthritis	.35
13	52	F	10	238/108, 80	CF, LBBB, HR, MRD	Obesity	.4
14	69	F	3	206/ 78, 78	CF, GAS, HR	Obesity	.35
15	43	F	5	220/138, 100	CH, LAD, QT, r.CVA, HR, MRD	Hypochromic Anemia	.4
16*	38	M	4	218/128, 84	CH, RAsp, PS 1 yr., MRD		.4
17	41	F	2	252/126, 92	CH, LAD, HR, SRD	Secondary Anemia	.4
18	38	M	9	192/124, 76	LAD		.4
19*	76	M	?	188/120, 96	LAD, LBBB, HR	Senile Dementia	.5
20	40	M	8	236/120, 68	CH, RAsp, PS 1 yr., MRD		.5
21	44	M	15	240/120, 77	CH, GAS, AR, MRD		.5
22	53	M	4	170/110, 78	LAD, HR		.5
23	58	M	10	210/110, 78	CH, LAD, H (o.CVA), HR		.4
24	45	M	10	188/110, 88	LAD, AR	Obesity	.5
25	41	M	5	240/108, 80	LAD, HR, MRD		.5
26	64	F	10	174/108, 80	LAD, GAS, GF, HR		.2
27	41	M	2	210/106, 100	CH, LAD, HR, SRD	Syphilis	.4
28	62	F	10	210/106, 72	LAD, GAS, HR	Obesity	.5
29	49	M	3	155/100, 76	CH, H, AR, HR, RAth, MRD	Syphilis	.5
30	58	F	3	250/105, 114	CH, LAD, HR, SRD		.25
31	34	F	2	180/100, 100	LAD, RAsp, R.TP	Obesity	.35
32	56	M	8	215/ 86, 88	LAD, PT, AR		.4
33	46	M	11	144/ 78, 52	LAD, HR		.45
34	39	M	1	192/110, 87	sl.CH, RAsp, MRD		.5
35*	68	M	10	235/140, 80	DA, QT, HR, MRD	Obesity, Peptic Ulcer	.5
36	39	M	1	262/130, 72	HR, MRD		.5
37	42	M	4	208/128, 64	GAS, HR, MRD		.4
38	67	F	2	180/120, 80	HR		.4
39	53	M	2	214/118, 90	GAS, AR, HR, MRD		.5
40	29	F	1/6	170/116, 70	MRD		.35
41	68	M	2	208/114, 72	GAS, o.CVA, HR	Ventral Hernia	.5
42	38	F	3	180/110, 95	Marked RAsp		.4
43	48	F	2	172/108, 88	o.CVA, MRD		.35
44	69	M	15	238/104, 68		Duodenal Ulcer	.5
45	53	M	5	164/ 98, 82	PT		.5
46	53	M	7	164/ 88, 84	GAS, HR		.5
47	80	M	?	168/ 72, 80	GAS, AR		.5

* Los Angeles General Hospital, the others being private patients.

AF: auricular fibrillation. AR: arteriosclerotic retinopathy. CF: congestive heart failure. CH: cardiac hypertrophy. CVA: cerebrovascular accident. DA: dilatation of aorta. GAS: generalized arteriosclerosis. GF: gangrene of foot. H: hemiplegia. HR: hypertensive retinopathy. IB: intraventricular block. LAD: left axis deviation. LBBB: left bundle branch block. MRD: moderate renal damage. o.: old. PS: paravertebral sympathectomy. PT: popliteal thrombosis. QT: prolonged QT interval. RAsp: retinal angiospasm. RAth: retinal angiothrombosis. r.: recent. SA: aortic stenosis. sl.: slight. SRD: severe renal damage. TP: toxemia of pregnancy.

diastolic pressure and pulse rates were similarly treated. Finally, since these three measurements obviously changed equally, both in individual patients and in the means of the group as a whole during the first two hours following medication, an average of the three was made. The results are shown in table 2.

It can be seen that the blood pressure and pulse readings fell on an average to about 83 per cent of their pretest readings (or were reduced by 17 per cent). Since the individuals were found to be normally distributed about their mean or average (both in the entire group and in the numerous subdivisions which were studied statistically), when arranged arithmetically, it is permissible to utilize the standard deviations shown in the table to estimate the probability that patients of this kind will exhibit a given percentage reduction as a result of similar treatment. For example, one patient out of 6 may be expected from these studies to have a reduction in blood pressure and pulse rate of less than 5 per cent; about one-half should have a reduction of at least 15 per cent; and one in 6 may be expected to show a reduction of 25 per cent or more. In view of the diversity of the group studied and in the findings noted it is not unlikely that these estimations may be good approximations of the effects of dihydroergocornine upon the pulse and blood pressure when administered in a single dose intravenously.

With respect to the possible effect of age upon the percentage reductions in blood pressure and pulse rate, no significant differences were found except in a very small group aged 70 years or more, where the drug had somewhat less effect than in those less than 70 years of age. However, in view of the smallness of the group and the absence of any age differences in the younger group, this finding should receive no undue attention. Similarly it was noted that in the small group of patients with severe renal damage the blood pressure and pulse rates fell somewhat more slowly than was the case in patients with less renal damage, but this difference was observed only at the first fifteen-minute interval and whether valid or not it would appear to be of little consequence.

With these exceptions, the response to the drug was not significantly influenced by age, sex, congestive heart failure, cardiac hypertrophy or left axis deviation, arteriosclerosis, angiospasm, degree of renal damage, dosage of the drug, the interval at which it was given, or the pretest level of the pulse or blood pressure when all calculations were based upon percentage change of the postinjection readings in relation to preinjection readings. The large individual variations observed in this series must therefore be ascribed to factors now unknown other than those just referred to.

TABLE 2.—*Effects of dihydroergocornine methanesulphonate* (DHO-180) *on the systolic and diastolic blood pressures and radial pulse rates, showing the mean percentage of the pretest reading* (*M*) *and the sample standard deviation,* (*S*), *for each measurement, and the average of the three types of measurement, at each time interval*

Per cent of Pretest Level

Time after Administering DHO-180	Systolic Pressure		Diastolic Pressure		Pulse Rate		Average of Systolic, Diastolic and Pulse Percentages
	M(%)	S	M(%)	S	M(%)	S	
15 minutes	90.2	*9.0*	92.8	*9.8*	91.2	*8.4*	91.4
30 "	82.1	*11.7*	87.9	*9.4*	86.5	*8.6*	85.5
45 "	81.8	*11.1*	87.5	*9.8*	86.5	*9.7*	85.3
60 "	82.1	*9.9*	86.5	*9.8*	82.3	*10.3*	83.6
75 "	83.0	*10.1*	85.9	*12.3*	82.7	*10.3*	83.9
90 "	83.2	*10.4*	84.3	*10.1*	83.8	*10.7*	83.4
105 "	82.8	*10.8*	87.7	*10.4*	82.8	*9.8*	84.4
120 "	83.6	*10.8*	86.5	*9.4*	83.8	*9.9*	84.6
24 hours	90.3	*10.2*	98.0	*13.7*	89.3	*9.7*	92.5

Ten patients of this series received dihydroergocornine on two or more subsequent days in dosage varying from 0.25 to 0.5 milligram. In these the reduction of blood pressure and pulse rate was similar to the change that took place in patients receiving the single injection. No concrete evidence of cumulative action was demonstrated in this group.

The oral use of dihydroergocornine failed to produce an appreciable reduction in the blood pressures or pulse rates of this group, irrespective of the dosage given (0.5 mg. to 15 mg. daily). In this group it was administered in both liquid and tablet form.

With respect to the toxic manifestations, 17 of the 47 patients observed in this series had no untoward symptoms. The remaining 30 sub-

jects exhibited one or more of the effects shown in table 3. It will be noted that a majority of these reactions consisted of a transient "nasal stuffiness" which in no way disturbed the patient. Only in two did we observe toxic manifestations which would be considered "alarming." These recovered spontaneously without additional medication. Definite predictions concerning the frequency of uncommon events cannot reliably be made from samples of this size. It can only be stated at this time that reactions do occur with the doses used. There is no evidence that any particular type of patient is more or less likely to develop toxic effects of this drug.

TABLE 3.—*Occurrence of various untoward reactions, showing the number of individuals exhibiting the indicated reaction out of the 47 patients treated with a single dose as indicated in table 1. Many of the individuals had two or more untoward effects; 30 patients had some reaction; 17 patients had no untoward effect.*

Nasal "stuffiness"	21
Dryness of the mouth	4
Nausea	3
Vomiting	2
Dyspnea	2
Syncope	2
Dizziness	2
Weakness	2
Faintness	3
Tingling	1
Lethargy	1
Sweating	2
Chills	3
Cold and clammy	1
Flushing	1
Feeling of warmth	3
Impaired vision	2
Delayed circulation	1
Headache	1
Sense of fullness in the head	1
Tenderness of breast	1

Follow-up laboratory studies revealed no change following the use of dihydroergocornine intravenously. Routine electrocardiograms recorded prior to and immediately after the two hour period of clinical observation reveal only a slight variation in the polarity of the T waves in one or more leads in approximately 10 per cent of the group. Conduction time remained unchanged as did other electrocardiographic components.

DISCUSSION

To be assured that only patients with sustained hypertension were chosen for this preliminary study, a careful historical survey was made on each patient and this was followed by daily clinical observation. Of the first 94 patients with hypertension studied, all but 18 were discarded since rest, induced sedation, and a low-sodium diet effectively lowered their blood pressures and pulse rates. The 47 patients accepted retained an appreciable elevation of their blood pressures after the institution of this regime. The 12 control patients utilized failed to demonstrate an appreciable lowering of the blood pressure or pulse rate yet subsequently the administration of dihydroergocornine intravenously produced an appreciable effect. Two patients included in this series had undergone unsuccessful paravertebral sympathectomies. In both we were able to demonstrate an appreciable reduction of both systolic and diastolic blood pressure and pulse rate following the use of dihydroergocornine. This effect would suggest the possibility of inadequate surgical section.

The data presented here together with evidence cited earlier indicates that dihydroergocornine intravenously has a depressor effect upon the blood pressure and a slowing effect upon the heart rate; that the percentage reduction in systolic pressure, diastolic pressure and pulse rate is the same for any given patient; and that this effect of a single dose is well maintained for at least two hours, and even persists for at least twenty-four hours so far as the systolic pressure and pulse rate are concerned. This result suggests that the hypertensive state in this group was at least partially induced through the action of pressor substances on the sympathetic system and that the vasodilator and vasoconstrictor centers played an important role in this mechanism. Inasmuch as it has been shown that dihydroergocornine acts in the main as a sympatholytic agent, the results obtained support the neurogenic mechanism of this syndrome. The slowing of the pulse is accomplished by the action of this drug on the vagus center. We have demonstrated the abolition of this effect by the administration of atropine to test subjects. The action of dihydroergocornine is unlike that of so-called

peripheral vasodilators in common use today. In these, vasodilatation is rapidly followed by cardiac acceleration. This action often produces a subsequent rise in arterial pressure which may increase the load on the heart. Because both a reduction of blood pressure and heart rate may appreciably reduce coronary flow, we feel that the use of dihydroergocornine is contraindicated in the presence of coronary artery disease.

The ineffectiveness of dihydroergocornine by the oral route is probably due to its destruction by gastrointestinal ferments. This contention seems to be supported by the preliminary studies of one of our co-workers.

Inasmuch as we were unable to demonstrate an appreciable cumulative effect by subsequent daily injections, we can assume that for the most part dihydroergocornine when given intravenously is entirely dissipated from the body within twenty-four hours.

Although toxic reactions were observed in 30 of the 47 patients, they were alarming in only a few. A proper estimate of the incidence of serious reactions, and their relationship to dosage can only be made from a much larger series of patients. Such reactions do not appear to be sufficiently frequent, however, to preclude further intensive study.

Summary and Conclusions

This preliminary study has demonstrated the sympatholytic effectiveness of a single dose of dihydroergocornine methanesulphonate, administered intravenously, to 47 patients with sustained arterial hypertension. The drug produced an average reduction in both systolic and diastolic blood pressures and pulse rate of 17 per cent or to 83 per cent of the pretest levels within a period of two hours.

Although untoward reactions may occur from its use, these do not appear to be sufficiently frequent or of such severity as to preclude further study.

This drug offers hope as a palliative measure for the treatment of arterial hypertension in as much as its sympatholytic action also embraces a slowing effect on the heart and a minimal cumulative effect.

It is felt that it may prove to be a valuable adjunct in the selection of suitable hypertensive patients for surgical palliation because of its central action and because of our experience with two patients in this series.

Acknowledgments

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The "Two-Step" Exercise Electrocardiogram in Functional Heart Disturbances and in Organic Heart Disease: The Use of Ergotamine Tartrate

By Arthur M. Master, M.D., Leon Pordy, M.D., Joseph Kolker, M.D., and Mortimer J. Blumenthal, M.D.

Patients with functional cardiac disturbances, including chest pain, may present electrocardiographic abnormalities (pronounced RS-T depressions and T-wave inversions) after the "2-step" exercise test which are indistinguishable from those found in organic heart disease. Ergotamine tartrate was employed intravenously in conjunction with "2-step" tests in 10 cases for the objective differentiation of functional from organic heart involvement. However, ergotamine was found to be contraindicated as a routine for this purpose because of its anginal-provoking properties. We have substituted dihydroergocornine (DHO-180), a newer, safer ergot alkaloid, in our further investigation of this problem.

The distinction between organic heart disease and functional heart disturbance is a very practical one. The usual means of investigation are not sufficient for this differentiation. Thus a physical examination, teleroentgenogram of the chest, fluoroscopy of the heart, and electrocardiogram which yield normal findings do not rule out the possibility of occlusive disease of the coronary arteries. In approximately 25 per cent of patients with coronary artery disease the results of these examinations are entirely normal.[1] Our personal experience has led us to believe that a typical history of angina pectoris, relieved by nitroglycerin, may occur even in patients with functional heart pain.

The "2-step" exercise electrocardiogram and the 10 per cent oxygen test are being used with increasing frequency for the diagnosis of coronary artery disease when all other findings are normal, particularly those of the resting electrocardiogram.[2, 3] Unfortunately, in a very emotionally unstable person, electrocardiographic abnormalities may appear even in such an objective examination as the "2-step" exercise electrocardiogram or the 10 per cent oxygen test. In other words, if the disturbance is functional, the electrocardiogram may be altered and altered in the same degree as it is in a patient with severe anginal syndrome due to coronary artery disease. Patients who are under severe mental or emotional tension and those suffering from anxiety neurosis or from severe neurocirculatory asthenia may have a positive "2-step" electrocardiogram.[4] The effect of emotion on the heart and on the electrocardiogram has been emphasized by a number of authors.[5, 6]

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Nordenfelt[7] used ergotamine tartrate parenterally for differentiating functional from organic alterations in the electrocardiogram. Wendkos and Logue[8] used the drug in the differentiation of "sympathicogenic distortions of the T waves" from those due to organic heart disease. Biörck[9] reported the reversal of the electrocardiogram to normal during hypoxemia tests performed after the injection of 0.5 mg. of ergotamine tartrate in 9 of 10 patients with functional heart disturbances.

Method and Results

Since the effect of ergotamine on the "2-step" electrocardiogram has not been investigated, we decided to study the action of this drug administered intravenously to 5 patients with definite occlusive disease of the coronary

arteries and to 5 patients in whom there was undoubted functional heart disturbance without any evidence of organic disease. In all 10 cases the "2-step" exercise electrocardiogram was abnormal.

Ergotamine is one of many pharmacologically active alkaloids derived from the fungus *Claviceps purpurea* and is available commercially as the tartrate salt in a 0.1 per cent solution (Gynergen-Sandoz-N.N.R.).* Ergotamine tartrate was administered intravenously in 0.3- to 0.5-mg. doses. After intravenous injection in all 10 patients the effects of ergotamine became marked in from fifteen to thirty minutes and lasted up to one hour or more. A drop in pulse rate of 20 to 30 beats per minute was common, along with a rise in blood pressure of 20 to 40 mm. of mercury in both systolic and diastolic levels. Increase in amplitude of T waves was observed in the majority of subjects following the ergotamine injection (fig. 1). This change, however, did not affect the interpretation of either the control or exercise electrocardiogram made following the administration of the drug.

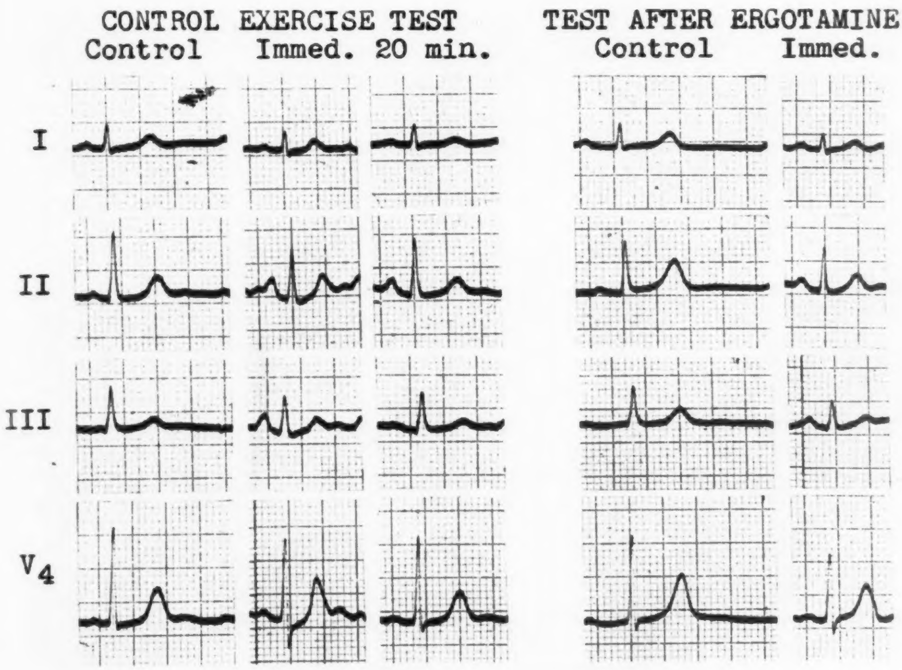

FIG. 1.—E. F. (Case 2, table 1), a woman, 30 years of age, had anxiety neurosis and atypical angina pectoris. The physical examination revealed no essential abnormality. The control electrocardiogram (made June 26, 1948) showed no abnormality, but immediately after the standard "2-step" exercise, RS-T depressions appeared in Leads V_4 and II. Ergotamine tartrate, 0.3 mg., was injected intravenously one hour later. The "2-step" exercise was repeated in fifteen minutes but no abnormal changes were noted in the electrocardiogram.

We chose 5 patients with functional heart disturbance (table 1) in whom physical examination, teleroentgenogram of the chest, and fluoroscopy of the heart demonstrated no abnormality. The electrocardiogram, consisting of the three standard limb leads, the augmented unipolar extremity leads (aV_R, aV_L, and aV_F), and the unipolar precordial

* The Gynergen for this study was kindly supplied by the Sandoz Company, New York.

TABLE 1.—*Ergotamine and the "Two-Step" Exercise Electrocardiograms: Functional Heart Disturbance*

Case	Age	Sex	History	Diagnosis	Physical Examination	Chest X-Ray and/or Fluoroscopy	ECG		Response to Nitroglycerin	Bl. Pressure	2-Step Test		Reaction to Ergotamine	Reaction to Anox. Test	Remarks
							Resting	Spontaneous Attack			Before Ergotamine	After Ergotamine			
1, L. F. N.	38	M	5 year history of frequent auricular premature beats and auricular paroxysmal tachycardia	Autonomic imbalance; anxiety state	Negative (Numerous premature beats and runs of tachycardia)	Negative	Negative			116/72	Positive $RS\text{-}T_{1,2}$; numerous premature beats	Negative and no irregularities of heart	Slight nausea, cramps in legs	Negative	
2, E. F. (see Fig. 1)	30	F	Angina pectoris-atypical; palpitation; hyperhidrosis; urinary frequency; emotional instability; hypochondriasis; generalized nervousness; cardiophobia	Severe anxiety state; spastic colitis	Negative (Moist palms; tachycardia; rt. thyroid adenoma-low B.M.R.)	Negative	Negative			118/84	Positive $RS\text{-}T_{1,2}$	Negative	Moderate nausea; vomited once	Positive	Anoxemia test negative after reassurance
3, M. T.	26	F	Angina pectoris-typical 5-year history; frequent palpitation; slight dyspnea; sexual maladjustment; cardiophobia	Anxiety state; old healed peptic ulcer	Negative	Negative	Negative	Negative	Variable relief at first	120/80	Positive $RS\text{-}T_1$	Negative	Severe nausea and vomiting	Positive	Psychiatrist's diagnosis: "severe anxiety reaction with psychosomatic conversion." Last G.I. series neg. for ulcer or hiatus hernia
4, H. S.	38	F	Paroxysmal tachycardia for 22 years; emotional instability; cardiophobia	Anxiety state; cardiac neurosis	Negative	Heart small, dynamic-pulsation	Negative			130/80	Positive $RS\text{-}T_{1,2}$	Negative	Severe nausea and vomiting	Positive	Anoxemia test negative after reassurance
5, H. M.	40	F	Angina pectoris-typical 5-year history; recurrent palpitation; easy fatiguability; cardiophobia; hysterical reactions; vertigo; (needs continual reassurance)	Anxiety state; cardiac neurosis	Negative (Hyperactive knee reflexes)	Heart small and vertical	Negative	Negative	Only occasional relief	148/84 to 158/94	Positive $RS\text{-}T_{2,3}$	Negative	Moderate nausea and vomiting	Positive (precordial pain during test)	

TABLE 2.—*Ergotamine Tartrate and the "Two-Step" Exercise Electrocardiogram: Coronary Heart Disease*

Case	Age	Sex	History	Diagnosis	Physical Examination	Chest X-Ray and/or Fluoroscopy	ECG		Response to Nitroglycerin	Blood Pressure	2-Step Test		Reaction to Ergotamine	Reaction to Anox. Test	Remarks
							Resting	Spontaneous Attack			Before Ergotamine	After Ergotamine			
6, S. H.	48	F	Angina pectoris-typical for 1 year	Arteriosclerotic and hypertensive heart disease. Chronic cholecystitis	Negative	Negative	Positive		Relief	116/82 to 160/100	Positive $RS\text{-}T_{4,\,2,\,1}$	Positive $RS\text{-}T_{4,\,2,\,1}$	Slight nausea for 24 hrs; vomiting twice	Negative	
7, B. N.	61	M	Angina pectoris-typical for past 1½ years—daily attacks at present	Arteriosclerotic and hypertensive heart disease (old posterior myocardial infarct)	Emphysematous chest	Negative	Negative	Positive	Relief	184/94	Positive $RS\text{-}T_{4,\,2,\,1,\,3}$ $T_{1,\,2}$	Positive $RS\text{-}T_{4,\,2,\,1,\,3}$ $T_{1,\,2}$	Belching	Positive	Anginal seizure 10 minutes after ergotamine injection with positive ECG changes and relief after nitroglycerin
8, E. T.	76	F	Angina pectoris-typical for 4 years	Arteriosclerotic heart disease	Negative	Negative	Negative	Positive	Relief	140/80	Positive $RS\text{-}T_{4,\,1,\,2,\,3}$	Positive $RS\text{-}T_{4,\,1,\,2,\,3}$	Slight nausea; no vomiting	Positive	
9, M. M.	55	M	Angina pectoris-typical for 5 years (osteoarthritis, severe, of dorsal spine, with reference of angina there)	Arteriosclerotic heart disease	Short apical systolic murmur	Negative	Negative	Positive	Relief	140/86 to 180/90	Positive $RS\text{-}T_{4,\,2,\,1,\,3}$	Positive $RS\text{-}T_{4,\,2}$	No nausea or vomiting		Two anginal seizures 10 and 30 minutes after ergotamine injection with positive ECG changes and relief after nitroglycerin. Angina following 2-step test before ergotamine
10, G. H. (see Fig. 2)	44	F	Angina pectoris-typical with reference of pain to jaw; dyspnea. Symptoms occurred 4 months following acute postcoronary occlusion	1. Hypertensive and arteriosclerotic heart disease (old coronary occlusion). 2. Diabetes mellitus	Negative	Moderately enlarged to left with paradoxical pulsation of left border	Positive		Relief	180/105	Positive $RS\text{-}T_{4,\,1,\,2}$	Positive $RS\text{-}T_{4,\,1,\,2}$	Moderate nausea		Moderate dyspnea and jaw pain after 2-step before ergotamine. Moderate dyspnea after 2-step after ergotamine

leads, V_1 to V_6, was normal. The age of these patients varied from 26 to 40 years; there were 4 women and only one man. The symptoms of these patients were those related to cardiac arrhythmias and tachycardias. Emotional instability, cardiac neurosis with cardiophobia, and anxiety states were common. Two patients (table 1, Cases 3 and 5) gave typical histories of angina pectoris and both obtained slight but variable relief from nitroglycerin.

The "2-step" exercise electrocardiogram showed positive changes in all 5 patients and the electrocardiogram made during the 10 per cent oxygen (anoxemia) test demonstrated positive changes in four of these patients. However, when the ergotamine tartrate (0.3 to 0.5 mg.) was given intravenously about thirty minutes before the "2-step" exercise test was repeated, in every instance the electrocardiogram made following exercise was of normal configuration. In other words, no RS-T depressions below the baseline or T-wave inversions appeared. This is illustrated by Case 2, in table 1, which refers to a woman physician 30 years of age with anxiety neurosis and a one-year history of atypical angina pectoris. Physical examination showed no essential abnormality. A control electrocardiogram was normal, but immediately after the standard "2-step" exercise the pattern was abnormal with RS-T depressions in Leads V_4 and II. Ergotamine tartrate (0.3 mg.) was

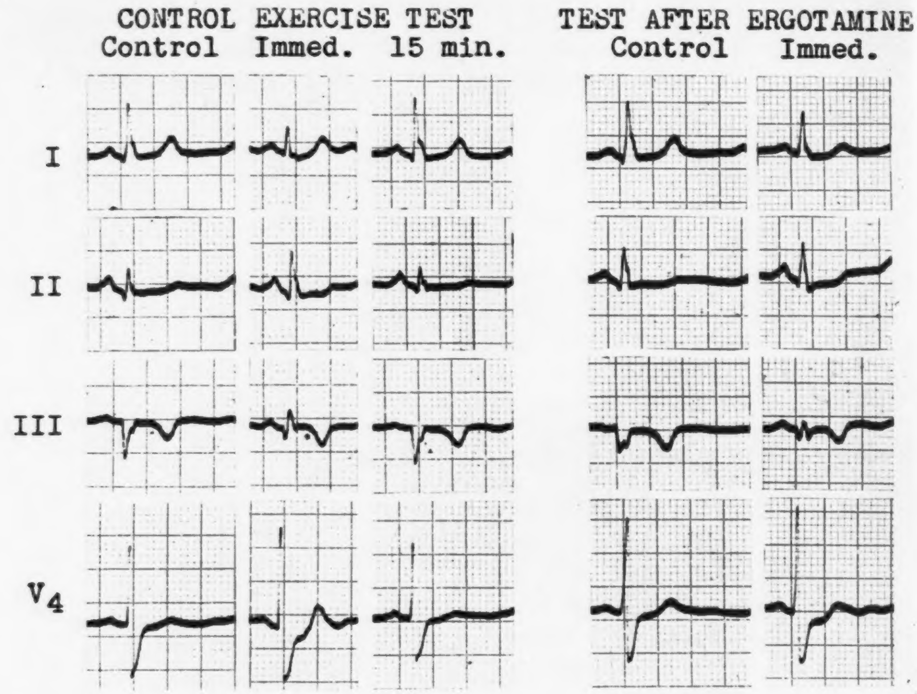

FIG. 2.—G. H. (Case 10, table 2), a woman 44 years of age, had an acute coronary occlusion one year previously. Control electrocardiogram made on April 28, 1948, showed Q-wave and T-wave changes in Leads II and III. Immediately after the standard "2-step" exercise distinct RS-T depressions appeared in Leads I, II, and V_4. On May 11, 1948, ergotamine tartrate, 0.5 mg., was injected intravenously and forty-five minutes later a repeat "2-step" exercise test revealed RS-T depressions similar to those of the control exercise test.

injected intravenously one hour later. After fifteen minutes, bradycardia and heightening of the T waves were noted; the "2-step" exercise was repeated, but no abnormal changes in the electrocardiogram occurred (fig. 1).

The 5 patients with organic heart disease (table 2) all revealed a typical anginal syndrome, with pain or pressure appearing after effort. Three of the patients were women and 2 were men. Their ages ranged from 44 to 76 years. Two of them had suffered coronary occlusions and four had hypertension. The resting electrocardiogram was abnormal in 2 (Cases 6 and 10, table 2). Electrocardiograms made during spontaneous attacks showed abnormality in all of these patients when opportunity for making these tracings during the episode of chest pain presented itself. Nitroglycerin brought relief to all.

In the group of patients with organic heart disease the "2-step" exercise electrocardiogram showed positive changes following the standard exertion, but in every instance when this was repeated after intravenous injection of ergotamine the electrocardiogram again showed abnormal patterns consisting of RS-T depressions and T-wave inversion. This is illustrated by Case 10, table 2, which refers to a woman 44 years of age with a history of acute posterior-wall myocardial infarction one year previously and a four-month history of typical angina pectoris and marked dyspnea. Her blood pressure was 180/105. The control electrocardiogram was abnormal with left-axis deviation and a QT pattern in Leads II and III. Immediately after the standard "2-step" exercise, distinct RS-T depressions in Leads V_4, I, and II appeared. Two weeks later, ergotamine tartrate, 0.5 mg., was injected intravenously and after forty-five minutes a repeat "2-step" exercise test showed abnormal electrocardiographic findings similar to those of the control exercise test (fig. 2).

The anoxemia test (10 per cent oxygen) was performed in all the 5 patients with functional heart disturbance and was positive in 4. The anoxemia test was positive in 2 of the 3 patients with organic heart disease in whom this procedure was essayed.

Comment

The observation of electrocardiographic abnormalities such as RS-T segment depressions and T-wave inversions, which occur spontaneously[8, 10] or during the hypoxemia test,[9] has been made several times in emotionally unstable individuals without organic heart disease. Certain authors have used ergotamine tartrate to prevent such changes.[7, 8, 9] We have also observed RS-T depressions and T-wave inversions following a standard "2-step" exercise test in such patients and have likewise prevented their appearance by means of ergotamine tartrate.

Some moot issues arise in the understanding of these facts. The exact mechanism of alteration of the electrocardiogram in the RS-T and T-wave segments of patients with functional disorders is unresolved. Lability of the autonomic nervous system has been thought by several investigators to be causally related to the electrocardiographic deviations in such patients.[7-10] The resemblance of the RS-T and T-wave patterns to those of coronary insufficiency suggests that reduced coronary blood flow may be responsible even in the patients with functional heart disturbances. Mainzer and Kraus[5] believe that psychic impulses acting through the autonomic nervous system cause coronary vasoconstriction with resultant myocardial anoxemia and RS-T and T-wave changes. Direct evidence for this is lacking in man. The present state of knowledge concerning the effect of the sympathetic and parasympathetic nerves on human coronary circulation does not permit a final answer. Recent animal work[11, 12] casts considerable doubt on the vasodilator actions of the sympathetic impulses on the coronary arteries.

Another mechanism which has been suggested to explain the electrocardiographic changes in functional heart disturbances is autonomic nervous system effect on cardiac action potentials by directly influencing cellular metabolism or membrane properties.[8] Scherf and Schlachman[13] state that direct sympathetic effects on the repolarization process occur. Various investigators have used drugs which act on the autonomic nervous system to abolish

electrocardiographic abnormalities in functional cases.[7, 8, 9] It seems that these electrocardiographic changes are closely related to the function of the autonomic, especially the sympathetic, nervous system. Although for years many investigators have been interested in this problem the precise influence in the electrocardiogram is not known.[14-16]

How ergotamine acts to prevent the RS-T depressions and T-wave inversions is another moot issue. In animals, experimental doses (0.1 mg. to 0.5 mg. per kilogram of body weight) possess strong sympatholytic and adrenolytic properties.[17, 18] In man, clinical dosage of 0.5 mg. produces effects not readily explained. There is evidence that it does produce some sympatholytic effects in clinical doses.[19, 20] Its direct vasoconstrictor action on the arterial tree, however, masks many of the sympatholytic properties. The precise result of injection of a clinical dose depends on the size of the dose and the tonus of the sympathetic system at the time of injection. These two factors determine the vasoconstricting action of ergotamine and a host of reflex changes which integrate the heart and peripheral vascular tree.[19]

Although we had previously assumed[4] that ergotamine tartrate prevented the electrocardiographic changes which followed exercise by sympatholysis, we now are of the opinion that this is problematic. If ergotamine were sympatholytic, according to the older concepts of coronary innervation it should favor coronary constriction. and would hardly tend to relieve the reduced coronary flow which has been postulated as a possible cause of the RS-T and T-wave deviations. Likewise the direct vasoconstrictor effect of ergotamine on the coronary circulation and the rise in blood pressure which increases the work of the heart both militate against the latter explanation. Obviously, the known effects of ergotamine which would tend to reduce the effective coronary blood flow are inadequate to explain its action in these functional cases unless one introduces another and independent effect on cardiac action potentials which can compensate, in healthy hearts, for all the factors tending to favor relative myocardial anoxemia. Its chronotropic effects (pulse slowing) suggest either a vagotonic action, sympathicolysis, a direct effect on the sinoauricular node, or a combination of these.

Amidst all these theoretic uncertainties, the results of the experiment are quite definite. Consistent differences in the electrocardiogram made following the "2-step" exercise test and after the injection of ergotamine were shown by patients with functional heart disturbances and those with organic heart disease. In the former the electrocardiogram remained unchanged while in the latter it still became abnormal after exercise. Sinus tachycardia, itself, may be associated with RS-T segment depressions and must be excluded as a possible cause of such depressions following the exercise test. Examination of figure 1, illustrative of a functional case, reveals that a physiologic tachycardia occurs on exercise before and after administration of ergotamine tartrate whereas RS-T depressions are present before but are absent after the administration of the drug. (Each complex in the illustrations represents a complete cardiac cycle from P wave to P wave.) Hence tachycardia per se is not responsible for the RS-T segment depressions in this case, nor in our other functional cases.

It must be emphasized that ergotamine tartrate, despite its apparent usefulness, is not recommended for the differential diagnosis of such cases because of its widely known ability[17] to precipitate anginal seizures in true organic heart disease; this occurred in 2 of the 5 patients with organic heart disease (table 2, Cases 7 and 9). In addition nausea and vomiting were frequent side reactions.

Further studies on the relationship of the vegetative nervous system and the electrocardiogram with the newer autonomic drugs may elucidate some of the problems raised in this discussion, and provide accurate, safe, clinical methods for distinguishing functional from organic heart disease. In view of the potential dangers associated with the use of ergotamine tartrate clinically, we are continuing our investigations using new, safer agents. Dihydroergocornine (DHO-180) shows promise in this field.

Summary

1. Individuals with severe neurotic complaints may exhibit electrocardiographic changes, following the "2-step" standard exercise test, indistinguishable from those of organic heart disease.

2. The "2-step" exercise tolerance test was performed in 10 patients with signs and symptoms referable to the heart both before and after the intravenous administration of ergotamine tartrate. In the 5 patients with functional disturbances the "2-step" test was positive before ergotamine administration but negative following it. In the 5 patients known to be affected with organic coronary artery disease, the "2-step" test was positive both before and after the ergotamine injection.

3. In psychoneurotic subjects, electrocardiographic aberrations may occur in the "2-step" exercise electrocardiogram; the exact mechanism of this is not known. The changes may be related to altered coronary blood flow, or to a direct effect of the autonomic nervous system on the electrical potentials of the heart or on cardiac metabolism.

4. Ergotamine, which prevents these functional electrocardiographic abnormalities, exerts its action in a manner as yet unknown. The side reactions to ergotamine tartrate given intravenously were nausea, vomiting, and also angina pectoris in 2 patients with coronary artery disease. The use of ergotamine is not recommended for differential diagnosis because of its angina-provoking properties in patients with definite coronary artery disease. Safer agents (dihydroergocornine-DHO 180) are being investigated with encouraging results.

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Influence of Saline, Papaverine, Nitroglycerin and Ethyl Alcohol on Electrocardiographic Response to Standard Exercise in Coronary Disease

By Henry I. Russek, M.D., Richard H. Smith, M.D., William S. Baum, M.D., Charles F. Naegele, M.D., and Frederic D. Regan, M.D.

Much disagreement exists regarding the value of vasodilator agents in the treatment of coronary disease. Opinions have largely been based upon observations of pharmacologic action of drugs in animals, uncontrolled clinical studies and analyses of a purely subjective index, that of pain, in patients with angina pectoris. A technic was devised, therefore, to study the modifying action of various drugs upon the electrocardiographic response to standard exercise. To have validity, the procedure could be carried out only in a patient showing constant electrocardiographic changes with each performance of the standard test. The present communication records the findings in such a patient who was studied in this manner.

IT IS routine procedure to employ vasodilator drugs in the treatment of coronary disease. Although pharmacologic evidence derived from animal experimentation[1–5] supports this practice, the influence of drug therapy upon coronary reserve remains a controversial issue. Some investigators[6, 7] have reported no significant difference between the effects of commonly employed vasodilators and inert medications. Others,[5, 8–10] using clinical methods based upon purely subjective criteria, have concluded that beneficial response follows the administration of some of these agents. Conclusions derived from such procedures may be strongly influenced by psychogenic factors and thus cannot be accepted unreservedly. Similarly, favorable effects previously attributed to various drugs in the treatment of coronary disease may have been the result of insufficient consideration of the natural course of angina.[6]

At the present time, clinical electrocardiography offers the most objective means of evaluating changes in the coronary circulation. Furthermore, it has been demonstrated that induced anoxemia in certain patients with coronary insufficiency is attended by appreciable electrocardiographic alterations.[11, 12] In such patients an opportunity might be afforded to study the modifying action of certain drugs.[13] The ideal subject for observation would be one in whom, under carefully controlled conditions, the use of a standard test would repeatedly produce electrocardiographic changes of the same order.

Having found a case fulfilling these criteria, an investigation of the comparative vasodilator effects of papaverine, nitroglycerin, and ethyl alcohol was undertaken, utilizing the Master "two-step" test.[12, 14]

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Case History

The patient selected for study was a 50 year old white merchant seaman, who presented a history of angina of effort since 1940, at which time he sustained a myocardial infarction. During the ensuing years, he pursued his usual occupation as an electrical engineer. Nitroglycerin afforded him relief from attacks of substernal pain, which occurred several times weekly. For the month prior to admission to the hospital he noted an increase in the severity and frequency of these episodes. For a few days preceding admission he was unable to walk more than a block without experiencing substernal oppression. Each attack lasted for a few minutes and was

relieved by rest or nitroglycerin. Family and personal past history were irrelevant.

Physical examination revealed a well developed, slightly obese white man. The left border of the heart was in the left midclavicular line. There was a soft systolic murmur of Grade 1 intensity at the mitral area. Normal sinus rhythm was present, with a rate of 80 per minute. Blood pressure was 170/90. The lungs were clear throughout. There was no evidence of decompensation. The remainder of the physical examination revealed no abnormality.

Reactions to Mazzini and Kahn tests were negative. The urine, blood count, and nonprotein nitrogen value were normal. Roentgenologic examination of the heart showed no abnormal findings. Electrocardiographic study revealed changes suggestive of left ventricular strain (fig. 1). Sedimentation rate was 15 mm. in one hour (Cutler).

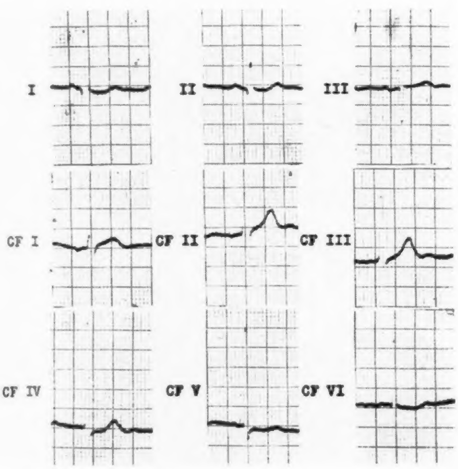

FIG. 1.—Control electrocardiogram of patient (limb and multiple chest leads).

Complete bed rest was instituted for a period of two weeks, following which time the patient became ambulant. There was appreciable clinical improvement as evidenced by increase of exercise tolerance. Serial electrocardiograms throughout the period of study revealed no significant changes. After one month of hospitalization the present investigation was undertaken.

Procedure

The patient remained under the standard hospital regimen, being up and about the wards daily. Tests were performed in the research electrocardiographic laboratory at precisely the same time each day, and by the same observers. Only one exercise test was performed in any twenty-four-hour period. Under these standard conditions the Master "two-step" test repeatedly showed RS-T segment depressions and T-wave changes of the same degree. Five such tests were recorded at varying intervals throughout the period of study. The materials used in testing were normal saline, papaverine hydrochloride, nitroglycerin, and ethyl alcohol. The standard exercise test was performed on consecutive days as follows: (1) five minutes after intravenous administration of 4 cc. of saline; (2) five minutes after intravenous administration of 4 cc. (2 grains) of papaverine; (3) sixty minutes after oral administration of 6 grains of papaverine; (4) ninety minutes after oral administration of 8 grains of papaverine; (5) five minutes after sublingual administration of 1/100 grain of nitroglycerin. (6) Twenty minutes after oral administration of 45 cc. of ethyl alcohol. Each test was performed on at least two different occasions.

Results

Inasmuch as the abnormal changes following the standard exercise test were in all instances most evident in the apical precordial lead (CF_4), tracings of this lead are presented immediately following exercise, and at two-minute intervals thereafter during a ten-minute period (fig. 2). The control Master test showed considerable depression of the RS-T segment amounting to 3 mm. immediately after exercise with progressive return to the resting control level after ten minutes. Although the T wave immediately after exercise was of increased voltage, subsequent tracings taken at two-minute intervals showed a varying degree of T-wave inversion, most marked in the four-minute tracing (where it was sharply inverted) with final return to an upright T wave at ten minutes. After four-fifths of the prescribed exercise had been performed, the patient experienced severe substernal pain lasting four minutes.

When the identical procedure was repeated five minutes after the intravenous administration of 4 cc. of saline,* a distinctly positive response was recorded, but of lesser degree than that observed in the control. Thus, the RS-T segment depression was 2.5 mm. after completion of exercise and thereafter closely followed the control pattern. Similarly,

* Intravenous tests employing saline and papaverine were performed by the "blind" technic, in which the agent used remained unknown to the patient and investigator until results were recorded.

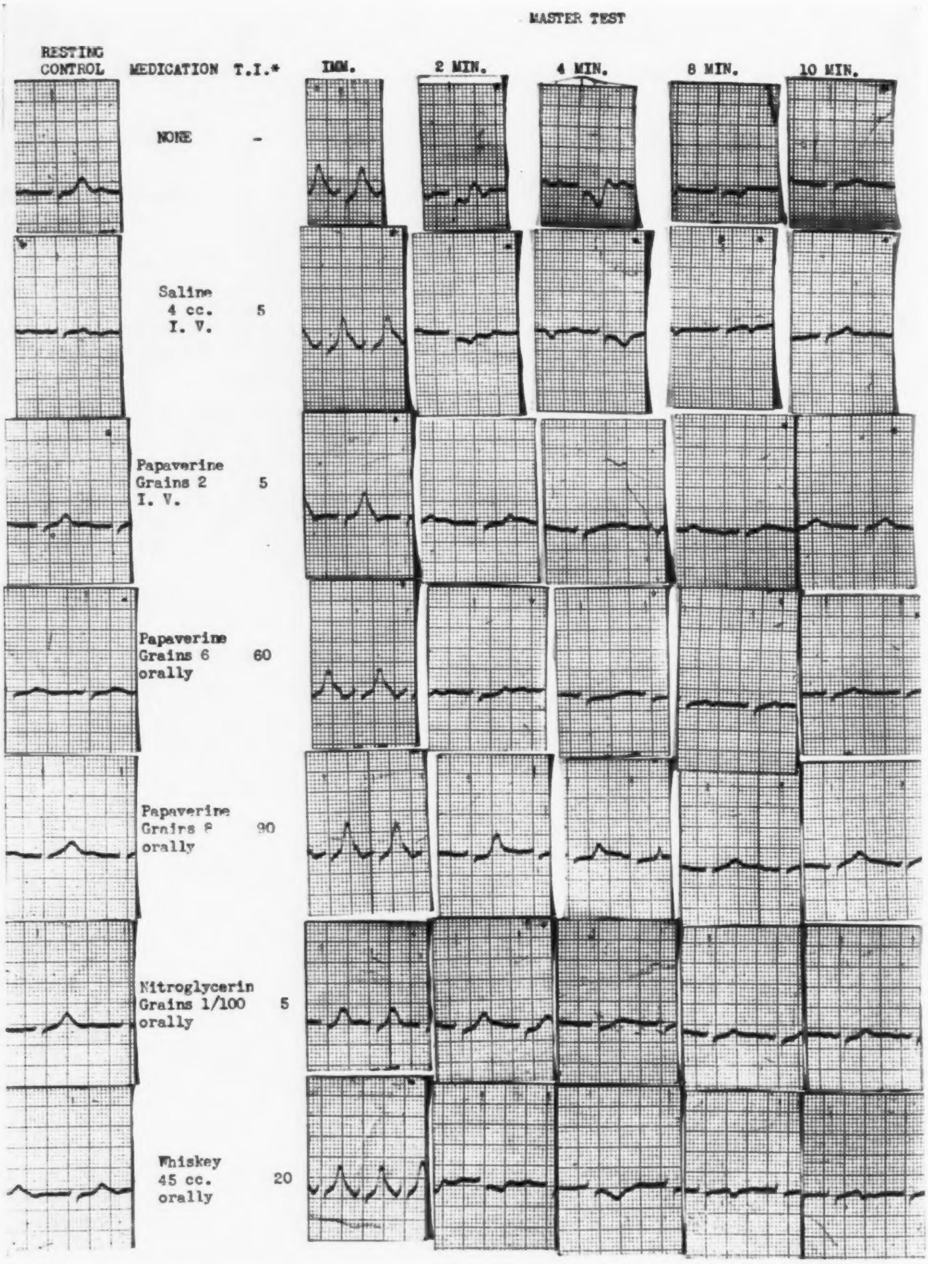

FIG. 2.—Tracings showing apical precordial leads (CF_4) obtained in performance of the Master test with and without the administration of various drugs.

* T.I., time interval (minutes) between medication and beginning of test.

significant T-wave inversion was also observed in the corresponding tracings although less pronounced than in the initial test. At the completion of exercise, the patient experienced mild substernal discomfort lasting one minute.

When the Master test was performed five minutes after the intravenous administration of 4 cc. (2 grains) of papaverine,* a distinct difference in the electrocardiographic response was observed. The RS-T segment showed little variation from the resting control level. The T wave was of increased voltage immediately after exercise, later diminishing in amplitude, particularly in the four- and six-minute tracings, but without ever showing inversion. The performance of the test was not associated with the usual sensation of pain.

Similar testing of the patient sixty minutes after oral administration of 6 grains of papaverine (in capsule form) revealed significant electrocardiographic changes which, however, were distinctly less marked than those observed without medication or following the intravenous administration of saline. The RS-T segment was depressed 1.5 mm. immediately following exercise, and gradually reverted to the resting control level. Correspondingly, the T wave was of increased voltage at first, diminishing thereafter to become slightly inverted in the four- and six-minute tracings, where the only significant change as compared to the resting control was observed. The patient experienced minimal substernal discomfort at the completion of exercise lasting one minute.

The electrocardiographic response to exercise ninety minutes after the oral administration of 8 grains of papaverine (in powder form) revealed a depression of 1.5 mm. in the RS-T segment initially with complete reversion to the resting control level in six minutes. T-wave inversion was not observed throughout the entire ten-minute period, although the T wave was of slightly lower voltage in the six- and eight-minute tracing as compared to the resting control. The patient experienced minimal substernal discomfort at the completion of exercise lasting one minute.

The initial tracing recorded when the Master test was performed five minutes after the sublingual administration of 1/100 grain of nitroglycerin, showed an RS-T segment depression of 1.5 mm.; subsequent tracings revealed a gradual return to the resting control level after ten minutes. The T wave remained upright throughout, although in the four-, six-, and eight-minute tracings it was of lower voltage. The patient noted no pain in this test.

The electrocardiographic response to exercise twenty minutes after the oral administration of 45 cc. of ethyl alcohol (rye whisky - 95 proof) showed a depression of the RS-T segment of 1.5 mm., with return to the resting control level in eight minutes. There was an initial increase in the voltage of the T wave, which subsequently became inverted, and remained so for the ensuing ten minutes. This response showed a similarity to the one previously recorded with intravenous saline. The performance of the test was associated with slight substernal pain at the completion of exercise, lasting two minutes.

Comment

The need for an objective method of evaluating the influence of so-called vasodilator drugs upon the coronary circulation has long been apparent. To obviate the errors attending methods utilizing purely subjective criteria, others[5, 8] have advocated the use of a "blind technic" for study. Although this approach seems to offer an accurate method for analysis, the electrocardiogram in certain selected subjects would appear to permit a more direct and objective measure of coronary circulation. The electrocardiographic response in certain normal individuals has permitted the human bio-assay of digitalis.[15] Similarly changes in the electrocardiogram in some patients with coronary disease seem to reflect quantitatively the degree of coronary insufficiency under normal and experimental circumstances.

The patient whom we selected for study repeatedly showed a relatively constant positive response to the Master "two-step" test under standard conditions. Control records were obtained at varying intervals throughout the period of study in order to exclude the possible influence of changes attending the natural course of the disease. Comparisons were

* See footnote, page 701.

made between these tracings and those obtained following the use of saline, papaverine, nitroglycerin, and alcohol. Comparisons were also made of the pain elicited in each instance. The results permitted a relative evaluation of the vasodilating properties of these agents, in the patient studied. It was found that the intravenous administration of 2 grains of papaverine had a marked modifying influence upon the electrocardiographic response to standard exercise. This effect was similar to that observed following the sublingual administration of 1/100 grain of nitroglycerin. With each of these agents, moreover, performance of the test was unaccompanied by pain. In contrast, the intravenous administration of 4 cc. of saline, and the oral administration of 45 cc. of whisky, respectively, produced only slight modification of the electrocardiographic patterns repeatedly observed in the control records. In both instances, mild to moderate pain was experienced at the completion of the exercise.

The dramatic response observed with the intravenous use of papaverine made it desirable to determine whether or not the administration of this drug by the oral route might also have significant effect. From previous clinical experience,[16] it was felt that relatively large oral doses of papaverine would be required for a measureable therapeutic response. This appeared to be further substantiated by our observations. Thus, performance of the standard exercise test one hour after the oral administration of 6 grains of papaverine (in capsule form) was attended by appreciably less significant alterations in the electrocardiogram than were observed in the control, saline, and whisky tests, respectively. Even more striking was the modifying influence of 8 grains of papaverine administered orally (in powder form), upon the electrocardiographic response to exercise. An effect was observed comparable to that seen with intravenous papaverine (2 grains), and nitroglycerin (1/100 grain), respectively. Particularly noteworthy is the fact that with oral dosage the action of the drug was apparent ninety minutes after its administration. There was, however, minimal substernal pain at the completion of exercise, when these oral doses of papaverine were employed in the manner described.

These observations seem to indicate that papaverine administered either by oral or intravenous routes had a distinctly favorable influence on the electrocardiographic response to exercise in the patient studied. In this connection, however, it is important to note that the oral and intravenous dosage employed was considerably in excess of the amount in general usage in the treatment of coronary disease. Nitroglycerin showed prophylactic value when employed several minutes prior to the commencement of the exercise test. The observations imply that whereas nitroglycerin had an immediate and transient effect, oral papaverine in the dosage used had a more delayed and prolonged action. Thus, in the latter instance, a distinctly favorable influence was apparent in the electrocardiographic records obtained ninety minutes after administration of the drug. In contrast, the administration of 45 cc. of whisky appeared to have negligible effect on the electrocardiographic response to exercise

Summary

Although widely employed in the treatment of coronary disease, the relative and actual potency of vasodilator drugs remains poorly defined. Considerable difference of authoritative opinion exists with respect to the value of identical therapeutic agents. A method is described which appears to afford a means of evaluating the action of some of these drugs upon the coronary circulation in man. The technic requires the study of selected patients with coronary disease who exhibit upon repeated tests under standard conditions a relatively constant positive response to the Master test.

Observations upon such a patient have disclosed that papaverine administered by the oral or intravenous route, in relatively large dosage, had a marked modifying effect upon the electrocardiographic response to standard exercise. The effect of 8 grains of oral papaverine ninety minutes after its administration was comparable to that of 1/100 grain of nitroglycerin after five minutes. Under similar

conditions, 45 cc. of whisky failed to produce significant alteration in the electrocardiographic records obtained following exercise.

Further studies of this nature in suitable subjects may supply valuable information with regard to the therapy of coronary disease.

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Observations on the Daily Changes in Venous Pressure and Weight in a Case of Chronic Congestive Heart Failure

By Walter Newman, M.D., and Leo Fishel, M.D.

A study of the effect of salt administration and digitalis withdrawal as separate factors in the production of congestive heart failure in the same patient is presented. The results indicate two different types of congestive failure relating to these modes of precipitation. Additional information is obtained as to the temporal precedence of weight and venous pressure in congestive heart failure induced by the aforementioned methods.

THERE have been many reports dealing with the pathogenesis of chronic congestive heart failure. The two concepts under investigation at present are the so-called "forward" and "backward" hypotheses. It has been reasoned that if temporal precedence for either weight or venous pressure could be established in a patient going into congestive failure, one would have further evidence to support one or the other hypothesis. Thus, Warren and Stead[10] demonstrated in 2 patients in whom congestive failure was precipitated by the administration of salt that the weight rose before the venous pressure. They therefore concluded that the elevation of venous pressure in chronic congestive failure was a resultant of salt and water retention. On the other hand, Reichsman and Grant[6] were able to demonstrate that the venous pressure rose before any gain in weight in those patients in whom the congestive failure was precipitated by discontinuing the administration of digitalis. The latter authors then conclude that these observations are compatible with the "backward" failure hypothesis, the cardiac edema being due mainly to increased venous pressure secondary to right heart failure.

It seemed to us that the two hypotheses for the pathogenesis of chronic congestive heart failure were not mutually exclusive. The discrepancy in the aforementioned results might be due to the operation of two different mechanisms. We therefore decided to repeat the work of these investigators and possibly demonstrate the operation of two mechanisms of congestive failure in the same patient. Accordingly, the same patient was used for both methods of producing cardiac failure, namely (1) the administration of salt and (2) the discontinuance of digitalis therapy.

Method

The patient was a 52 year old Negro with auricular fibrillation and known hypertensive and arteriosclerotic heart disease of six years' duration. He had had five admissions to the hospital for the treatment of congestive heart failure in the preceding four years. In order to maintain compensation and a baseline weight between 155 and 162 pounds while ambulant, the patient was kept on the rice diet, received 4 grams of ammonium chloride daily, 1 cc. of Mercuhydrin intramuscularly three times a week and 0.5 mg. of Digoxin daily. Measurements of weight and direct venous pressure determinations were done daily and the patient was examined for signs of congestive heart failure. After a baseline was established, 5 grams of oral sodium chloride were given daily for five days; the sodium chloride was then continued but Mercuhydrin and ammonium chloride were discontinued. Following the appearance of signs of congestive failure, the sodium chloride was stopped and ammonium chloride and mercurial therapy were readministered. When compensation was restored, Digoxin was discontinued and when the signs of congestive failure supervened an unsuccessful attempt was made to regain compensation by increasing the frequency and dosage of mercurial

From the Cardiac Service, Veterans Administration Hospital, Bronx, N. Y.

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injections. Finally, mercurials were discontinued and digitalis was readministered.

The venous pressure was determined with the patient in the supine position, a small pillow supporting his head. A level, attached to the apparatus holding a manometer and reservoir of sodium citrate, was so adjusted that when it rested on the patient's sternum the zero point of the manometer was 5 cm. below its level. The arm used was elevated by a pillow to the zero point of the manometer and abducted 45 degrees.

The manometer was filled to the top (400 mm.) with sterile citrate from the reservoir and then with the tubing attached and the reservoir closed off, the basilic vein was entered with an 18-gage needle and the citrate was permitted to flow into the vein. The patient was allowed to rest in the supine position for fifteen minutes before the venous pressure was determined. By refilling the manometer from the reservoir, repeated readings were made until three successive determinations were within 5 mm. of each other. The average of these three readings was recorded as the venous pressure of that patient at that time.

Results

The results obtained are listed in table 1 and figure 1. We were able to demonstrate that the administration of sodium chloride to this patient was accompanied by a 16 pound gain in weight and 159 mm. of water increase in the venous pressure in twelve days. Both of these variables rose simultaneously without one preceding the other. When the sodium chloride was discontinued and the Mercuhydrin and ammonium chloride therapy reinstituted, the weight and venous pressure fell simultaneously to their baseline levels.

When the Digoxin was discontinued, it was observed that in five days there was no gain in weight but an increase in the venous pressure of 122 mm. of water.

When the patient's venous pressure had reached its peak after discontinuance of Digoxin, an attempt was made to return it to its baseline with increased dosage and frequency of mercurial injections. This was at first successful, with weight and venous pressure falling simultaneously. Then, despite the continued administration of mercurials, the weight and venous pressure began to rise and Digoxin therapy was readministered, mercurials and ammonium chloride being discontinued. The ventricular rate, which had risen following cessation of digitalis therapy, dropped precipitously with the venous pressure when the patient was redigitalized. The weight, however, did not fall with digitalis administration and in the last week of the experiment the patient gained 7 pounds. This gain in weight was attributed to increased ingestion of sodium, since the rice diet was discontinued during this period.

Two further points on the curve are worthy of mention. From January 30 to February 2 the patient was permitted to leave the hospital, and during this period he indulged in an excessive amount of exertion as compared with the ambulant regimen in the hospital. It is to be noted that following return to the hospital there was a striking rise in the venous pressure without any increase in the weight. A similar situation occurred between March 30 and April 1. On February 14, the drop in weight and venous pressure below the baseline, following salt and mercurial administration, suggests that some degree of sodium depletion existed prior to the initial administration of salt.

The patient was considered an excellent observer and despite the vagaries of subjective responses it was felt that they were of definite value in this experiment. While the patient was receiving salt from February 14 to February 24, despite marked increases in the weight and venous pressure, he was asymptomatic. In striking contrast was the situation which obtained while the patient was not receiving digitalis. At this time, orthopnea, bouts of paroxysmal nocturnal dyspnea and dyspnea on only mild exertion became apparent. At first these symptoms could be controlled by increasing the frequency and dosage of mercurial injections; however, with this treatment the symptoms shortly recurred, the patient complained of severe thirst and digitalis had to be readministered.

At no time during the procedure were the patient's fluids restricted. Blood pressure remained relatively constant at about 180/120. There was laboratory evidence of renal impairment; maximum specific gravity of the urine was 1.015, urinary albumin varied from negative to 1 plus, and phenolsulfonphthalein excretion was 50 per cent in two hours.

TABLE 1.—*Variations in Weight, Venous Pressure and Ventricular Rate with Changes in Medication and Salt Administration in Patient with Chronic Congestive Heart Failure*

Date	Weight	Venous Pressure	Medications				Diet	Remarks
			Digoxin (mg.)	Ammon. Chl. (Gm.)	Mercuhydrin (cc.)	NaCl (Gm.)		
1/29	159¾	124	0.5	4	1		*	
1/30	162	128	0.5	4	1		*	On pass 1/30 to 2/2 with increased exertion.
2/2	160	196	0.5	4	1		*	
2/3	160½	190	0.5	4			*	
2/4	159½	110	0.5	4	1		*	
2/5	158¼	120	0.5	4			*	
2/9	161	126	0.5	4	1	2	*	
2/10	159¼	121	0.5	4		5	*	
2/11	162	144	0.5	4	1	5	*	
2/12	159	139	0.5	4		5	*	
2/13	159¾	116	0.5	4	1	5	*	
2/14	155¼	94	0.5			5	*	
2/16	157½	114	0.5			2/15 5		
						5	*	
2/17	160¼	137	0.5			5	*	
2/18	161¾	130	0.5			5	*	
2/19	165½	197	0.5			5	*	
2/20	164¾	216	0.5			5	*	
2/21	164¾	220	0.5			5	*	
2/24	168¾	230	0.5			2/22 5		
						2/23 5	*	
						2/24 5		
2/25	171	253	0.5	4	1		*	
2/26	165¼	171	0.5	4			*	
2/27	167¼	203	0.5	4	1		*	
2/28	165	165	0.5	4			*	
3/1	166½	185	0.5	4	1		*	
3/2	163	157	0.5	4			*	
3/3	164¾		0.5	4	1		*	
3/4	163		0.5	4			*	
3/5	162¾	143	0.5	4	1		*	
3/8	163½	146	0.5	4	1		*	
3/9	159½	105		4			*	
3/10	161½	131		4	1		*	
3/11	162½	123		4			*	
3/12	163¼	159		4	1		*	Cough.
3/13	162	193		4			*	Dyspnea.
3/14	163¼	227		4	2		*	Severe dyspnea on exertion. Orthopnea.
3/15	162	185		4	1		*	Marked improvement in dyspnea and orthopnea.
3/16	159¼	132		4	2		*	Asymptomatic.
3/17	160	130		4	1		*	
3/18	157	123		4	2		*	Marked thirst.
3/19	158	140		4	1		*	Paroxysmal nocturnal dyspnea.
3/20	161	175					*	Paroxysmal nocturnal dyspnea.
3/21	161¼	171	2.25				*	Very dyspneic and orthopneic.
3/22	163	119	0.75				*	Marked improvement in dyspnea and orthopnea.
3/23	162¼	126	0.75				*	
3/24	161½	109	0.75				*	
3/25	162½	122	1.0				*	
3/26	162½	104	1.0				*	

TABLE 1.—*Continued*

Date	Weight	Venous Pressure	Medications				Diet	Remarks
			Digoxin (mg.)	Ammon. Chl. (Gm.)	Mercuhy-drin (cc.)	NaCl (Gm.)		
3/27	161½	108	1.0				*	
3/28	162½		1.0				†	
3/29	165¾	128	1.0				†	
3/30	165	127	1.0				†	
4/1	166	160	1.0				†	On pass 3/30 to 4/1, increased exertion.
4/2	163¾	104	1.25				†	
4/3	162¾	107	1.25				†	
4/5	168		1.25				†	
4/6	168¼	157	1.25	4	2		†	
4/7	157¼	76	1.25				†	

* Rice diet.
† Regular diet.

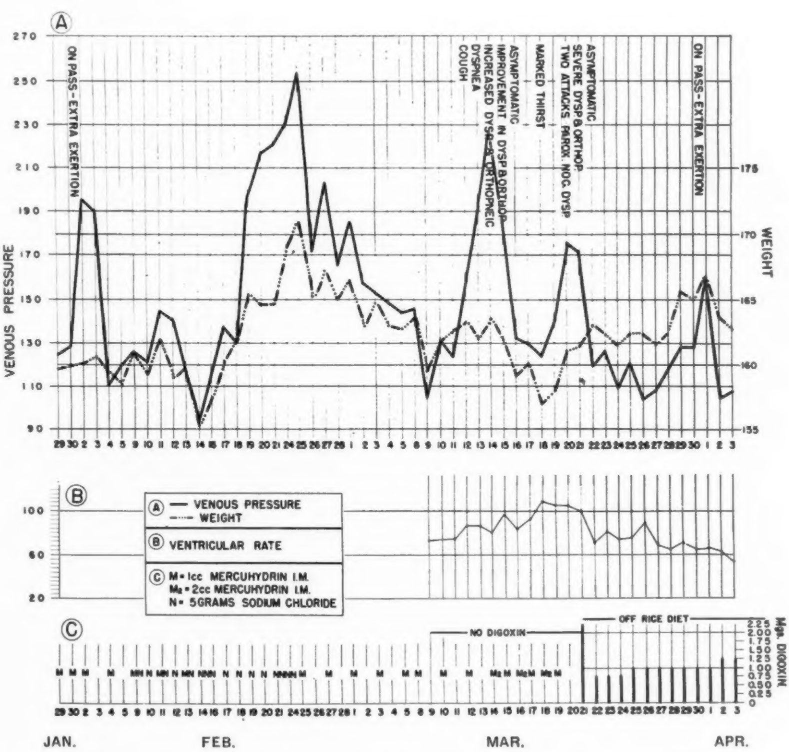

FIG. 1.—Graph illustrating variations in weight, venous pressure and ventricular rate with changes in medication and salt administration.

Discussion

Regarding the pathogenesis of the congestive failure in this patient, the following facts were established. When failure was induced by the administration of salt, weight and venous pressure increased simultaneously as noted in daily measurements. Similarly, in regaining compensation, weight and venous pressure fell simultaneously. Therefore, this experiment did not permit deductions based on the temporal relations of weight and venous pressure and concerning the mechanism of formation of cardiac edema.[10] Perhaps more frequent determinations might establish temporal precedence for one of these factors. These results were quite different from those of Warren and Stead,[10] who found that the weight rose before the venous pressure.

On the other hand, when failure was induced by the cessation of digitalis therapy, we found the venous pressure rose without any gain in weight. This result is quite similar to the observation of Reichsman and Grant[6] who demonstrated under similar circumstances "a considerable rise of venous pressure with no or very slight gain in weight."

The clinical status of the patient was quite different when failure was induced by the administration of salt as compared with failure induced by cessation of digitalis therapy. Whereas there was an increment in both weight and venous pressure in the former instance, the patient was relatively asymptomatic. However, in the latter instance, with no increase in weight and a definite rise in venous pressure there was a striking appearance of symptoms of dyspnea and orthopnea. This discrepancy in symptomatology and weight gains for comparable gains in venous pressure appears crucial and suggests two different mechanisms for congestive failure in the same patient. The first mechanism appears to be one of salt and water retention with equal distribution of fluid throughout the extracellular space. This would be analogous to the "forward" failure theory of formation of cardiac edema.[1, 10, 11] The second mechanism would appear to be one which is more acute and in which the myocardium must play the dominant role. It is suggested that this second mechanism, manifested by paroxysmal nocturnal dyspnea, orthopnea and increasing venous pressure with no increase in weight, is due to brief periods of discrepancy between the outputs of the right and left ventricles. This, then, produces a flooding of the lungs with attendant decrease in vital capacity and dyspnea. This concept of inequality in the outputs of the two ventricles with its resultant mechanical disturbances has been postulated by Harrison[3] and more recently by Stead.[8] It is also possible that there is more than one method of initiating this second mechanism. Thus, discontinuing digitalis in a myocardium that requires it, physical stress,[4] or even the stress of an infection or psychic disturbances,[9] may all be initiating factors. Finally, it would seem possible that the first mechanism, with its attendant hypervolemia, could increase the work of the myocardium enough to set off the second mechanism.

It is likely that the majority of patients one sees in congestive heart failure have both of these mechanisms operating. In view of the above observations, we cannot subscribe to the therapy of congestive heart failure outlined by Gold and his co-workers[2] where the initial and, if possible, sole use of mercurials is advocated. It is felt that in both of the suggested mechanisms, myocardial weakness is the primary factor. Therefore, digitalis would appear to be the rational initial drug of choice with mercurials and salt restriction considered as adjuvant measures. This thesis is given further support by the work of Merrill,[5] in some of whose cases clinical improvement of congestive heart failure by the use of mercurials was not associated with any marked increase in renal blood flow or cardiac output. On the other hand, Seymour and co-workers[7] were able to show that when cardiac compensation was restored by digitalis, cardiac output and renal blood flow increased.

Summary

Cardiac failure was precipitated in a patient with chronic congestive heart failure secondary to hypertensive and arteriosclerotic heart disease. Administration of salt and then cessation

of digitalis therapy were the methods used for initiating the failure. The following facts were established:

1. Weight and venous pressure rose simultaneously when failure was precipitated by salt administration and fell simultaneously when salt administration was stopped. When digitalis was withheld, there was a comparable rise in venous pressure but no rise in weight.

2. There were clear-cut differences between the failure induced by the administration of sodium chloride and that induced by discontinuing digitalis. (a) In the former instance there was a marked rise in both weight and venous pressure; whereas in the latter, for an almost comparable rise in venous pressure there was no increment in weight. (b) There was no dyspnea associated with the failure induced by salt; this was a prominent symptom when digitalis was discontinued. (c) The failure produced by discontinuing digitalis could not be controlled by increasing the dosage and frequency of mercurial administration.

Thus, two distinct types of cardiac failure were demonstrated in the same patient. Speculation as to the mechanisms of these two types of failure has led to the suggestion that the first type is due to salt and water retention with equal distribution throughout the extracellular space. Nothing could be added to the current knowledge of the mechanism of this retention. The second type of failure is believed to be a more acute variety and due to brief periods of discrepancy between the outputs of the two ventricles with subsequent redistribution of fluid on the venous side.

Finally, it is suggested that the majority of patients in congestive heart failure are demonstrating both mechanisms of heart failure. The use of digitalis rather than mercurials as initial medication is a more rational approach in the light of our present knowledge.

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Sensitivity of the Supraventricular Pacemakers to Acetylcholine in Acute Hypoxemia

By C. Callebaut, M.D., S. Rodbard, M.D., and L. N. Katz, M.D.

Severe hypoxemia enhances the effect of endogenous and exogenous acetylcholine to depress the supraventricular pacemakers and conduction pathways, as shown in experiments on dogs.

During acute hypoxemic states which are observed clinically during anesthesia and on exposure to high altitudes, cardiac irregularities including various degrees of block may be seen. The mechanism of these irregularities has not been adequately elucidated. It is known that early in hypoxia an increase in sympathetic tonus is seen[1]; late in hypoxia, however, the effect of epinephrine and other sympathetic mediators may be inhibited.[2,3] Under such conditions, augmentation of unopposed parasympathetic action might easily lead to cardiac slowing and to various degrees of heart block.

In the normal animal, injection of acetylcholine results in various degrees of depression of the sinus node ranging from sinus bradycardia to sinus standstill, with or without the occurrence of A-V nodal rhythm. The A-V conduction system is also depressed, causing A-V block and the appearance of idioventricular rhythms.[4] This effect of acetylcholine is enhanced in anemia.[5] Other workers have demonstrated that asphyxia increases the likelihood of auricular fibrillation on injection of mecholyl (acetyl-beta-methylcholine).[6] The present studies were undertaken in an effort to analyze the mechanism of heart block produced by this parasympathomimetic action occurring during acute hypoxemia.

Methods*

A total of 15 dogs were used. Thirteen were anesthetized with intravenous sodium pentobarbital (25 mg./Kg.); of these 8 were vagotomized bilaterally, and in 5 the vagi were left intact. In addition, two dogs with intact vagi were anesthetized with chloralose (100 mg./Kg.) and morphine sulfate (0.8 mg.) administered intravenously. After tracheotomy the thorax was opened by retraction of the ribs. Positive blast respiration was used. In this way the shift from air to nitrogen breathing could be accomplished in a second or two. At the end of hypoxemia periods, which lasted up to four minutes, air was again substituted for the nitrogen. Blood pressure from a femoral artery was recorded on a kymograph by means of a mercury manometer. Under fluoroscopic control a Cournand catheter was inserted through the left femoral artery into the left ventricle, the tip being directed toward the sinuses of Valsalva. In this way the acetylcholine used to determine sensitivity could be injected in apposition to the coronary ostia, thus eliminating to a large degree the variable factors of dilution in the pulmonary circuit, destruction in transit, and variability of delivery to the coronary arteries during left ventricular ejection. After each injection the catheter was flushed out with isotonic saline. Standard limb leads and occasional esophageal lead electrocardiograms were recorded on a direct-writing Viso-cardiette. A record was taken before hypoxemia and at various intervals during nitrogen breathing and during reoxygenation. Acetylcholine was injected via the catheter at intervals of thirty and sixty seconds or more of nitrogen breathing and the electrocardiographic response noted, particular attention being paid to the occurrence of heart block.

Since the P wave is sometimes relatively difficult to define and its beginning may not be easily seen, the R–R interval was used as a measure of heart rate whenever sinus rhythm was seen. R–R was also used in A–V nodal rhythm and in first-degree A–V block. In the few instances in which complete A–V block was produced the effect of the acetylcholine was determined by P–P distance. Increases in R–R (and P–P) distance measured to 0.01 second were used to determine the effect of each acetylcholine dose on the heart. At the end of each experiment the position of the catheter in relation to the sinuses of Valsalva was checked anatomically by opening the aorta. In the experiments discussed below, the catheter was

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found to be at or near the sinuses of Valsalva or in the left ventricle.*

Results

Heart Rate in Acute Hypoxemia. The cardiac response to hypoxemia depends in large measure upon the relative tonus of the sympathetic and vagus nerves. This was demonstrated by a comparison of the effects of two types of anesthesia: (1) nembutal, which reduces vagal tone through central inhibition and results in an increased heart rate, and (2) chloralose-morphine, which produces an increase in the activity of the vagal centers, and usually though not always slows the heart rate.

In intact nembutalized dogs, the induction of hypoxemia often produced a slight transient acceleration of the heart rate, but in nearly every instance the rate was slowed as the hypoxemia progressed (fig. 1). For example, a control rate of eighty-one per minute increased to ninety-three at sixty seconds of hypoxemia, and then slowed progressively to sixty beats per minute at the end of two hundred and twenty seconds of nitrogen breathing, sinus rhythm being present throughout. Further slowing of the sinus node frequently led to the occurrence of A-V nodal rhythm.

In the dogs with vagi intact, anesthetized with chloralose-morphine, the accelerator phase in early hypoxemia was much less apparent and the slowing was very marked, with a shift of pacemaker occurring early in every instance (fig. 1). These experiments had to be terminated early because of the marked irregularity of the heart with shift in pacemaker, and a resultant unreliability in the interpretation of effect on the electrocardiogram.

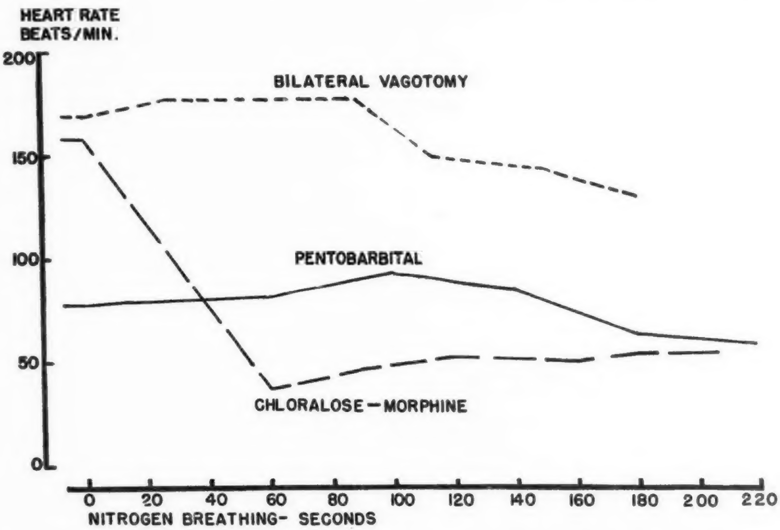

Fig. 1.—Effect of progressive hypoxemia on the heart rate under various circumstances. (Discussed in text.)

When the vagi were sectioned and the central parasympathetic tone eliminated, the action of the anesthetic agent on the parasympathetic system was no longer apparent. In these cases, the first effect of hypoxemia was a slight acceleration of the heart rate followed by a slight or moderate slowing (fig. 1).

Determination of the Threshold. In dogs breathing air, acetylcholine was injected in various amounts in order to determine the least amount necessary to produce a transient second-degree A-V block, as indicated by the occurrence of at least one blocked beat. This amount was called the *threshold dose* and it

*In one experiment an acute myocardial infarction was seen post mortem, possibly produced by the catheter.

varied considerably from one animal to another being 10 to 100 gamma in various experiments.

In the presence of hypoxemia, a threshold dose produced a greater degree of block. We therefore use subthreshold doses of the order of one-third to two-thirds the threshold dose. These subthreshold doses did not produce second-degree A-V block during air breathing, but before and after each hypoxia period. In a very few instances administration of a subthreshold dose of acetylcholine at the end of the reoxygenation period resulted in the production of A-V block. Data collected during the previous test were therefore not included in the present study because of the changing baseline during the course of such experiments.

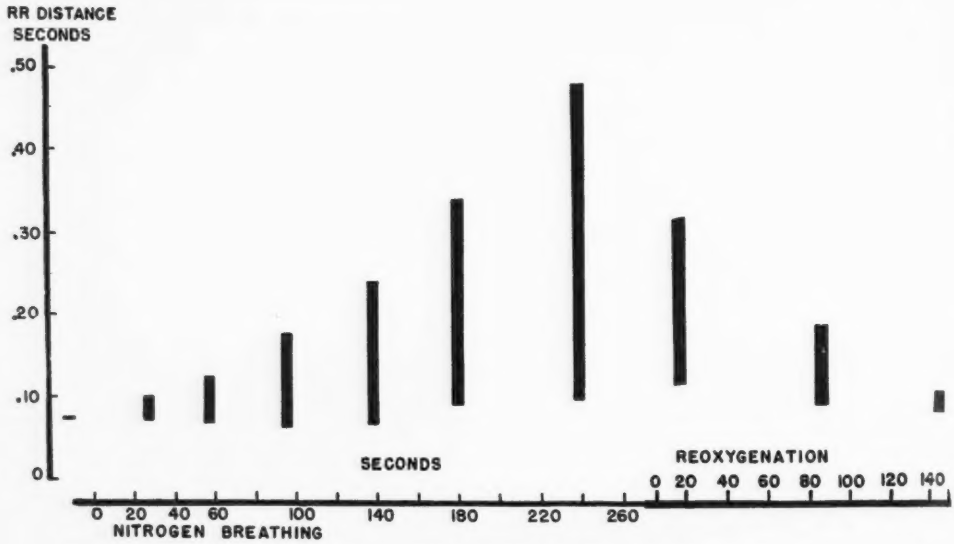

FIG. 2.—Acetylcholine sensitivity in acute hypoxemia and reoxygenation. A typical experiment showing the increased sensitivity to 20 gamma of acetylcholine in acute hypoxemia, and the rapid return to control values during reoxygenation. The value at the lower end of each column represents the R-R interval previous to acetylcholine injection. The value at the upper end of the column indicates R-R within one to three seconds after injection. The distance between these two values represents the magnitude of the heart block produced. (Discussed in text.)

were adequate to influence the sinus rhythm and produce a minimal slowing of the heart in the hypoxemic state.

As the experiment on each preparation continued, a progressive increase in sensitivity to acetylcholine was noted. As a result, doses which were subthreshold early in the experiment later acquired a blocking effect. The threshold dose was therefore decreased gradually as the experiment progressed. After several hours there was a tendency to develop a rather constant threshold.

To exclude the effects of slight spontaneous and temporary changes in threshold, the effect of a subthreshold dose was carefully checked

Sensitivity to Acetylcholine in Acute Hypoxemia. Sensitivity was estimated in terms of the increase in the duration of the R-R (P-P) distance which occurred within one to three seconds after administration of acetylcholine. No significant differences were noted in the degree of sensitivity change in the animals receiving either nembutal or chloralose-morphine anesthesia. Vagotomy also did not change the response. For this reason all experiments are discussed as a single group (fig. 2). The results with each group are given in table 1.

The response during the hypoxemia period in 75 per cent of instances was a progressive increase in sensitivity to acetylcholine. In 20

per cent a bidirectional effect was seen, in that at some point during the hypoxemic period a tendency to a transient decrease in sensitivity was noted; however, in all of these, the sensitivity at the end was always greater than at the beginning of the hypoxemic period. In 5 per cent of the experiments a marked increase in sensitivity was seen early, and this was followed by a progressive decrease in acetylcholine sensitivity during the hypoxemia period; in every instance, however, the final sensitivity was greater than the control. The animals anesthetized with chloralose-morphine were particularly sensitive to acetylcholine, as

TABLE 1. *Results of Tests of Sensitivity to Acetylcholine in Acute Hypoxemia*

Anesthesia	Vagi	No. of Experiments	Changes in Sensitivity		
			Progressive Increase	Bidirectional	Progressive Decrease
Pentobarbital	Intact	15	10	5	0
Pentobarbital	Cut	30	22	5	3
Chloralose-morphine	Intact	7	7	0	0

could be seen from the fact that the hypoxemia, even without further injection of acetylcholine, often resulted in marked bradycardia and the production of nodal rhythm. After one or two hypoxemic episodes these animals showed poor recovery and for this reason fewer studies were done on these preparations.

These results demonstrate that hypoxemia produces a progressive increase in sensitivity to acetylcholine. That this is not dependent only upon a central effect is shown by the fact that the increase occurs in the absence of central nervous connections, as in the vagotomized animals. The effect of hypoxemia must therefore be to increase the sensitivity of the receptor substance or to inhibit choline esterase.*

Sensitivity to Acetylcholine During Reoxygenation. At the end of each hypoxemia period the animals were returned to oxygen breathing. During this reoxygenation period the accumulated sympathomimetic substances which were not metabolized during the hypoxemia phase, once again have an effect, as can be shown by a marked increase in blood pressure.[2] During this period the sensitivity to acetylcholine is always rapidly returned to the control level within one to three minutes (fig. 2). This return of sensitivity appears to be independent of the blood pressure changes. Vagotomy had no significant influence on the rate of return to normal sensitivity. The decrease in sensitivity may be due to the sudden resurgence of epinephrine and sympathomimetic activity which had been in abeyance during the period of marked hypoxemia.[2] The possible role of potassium which has been shown to be released during anoxia must also be considered.

DISCUSSION AND CONCLUSIONS

Earlier workers have reported that the results obtained with large doses of mecholyl were unpredictable, the reaction to the same dose in a single experiment varying without apparent reason.[8] In their hands, hypoxemia did not alter the effect of mecholyl on the cardiac mechanism. A possible explanation of their results is that injection into a systemic vein might easily result in a variable delivery of the drug to the coronary vessels. Our experiments obviated this difficulty in large measure by delivery of very small quantities of acetylcholine directly to the region of the coronary ostia, and resulted in considerable consistency from injection to injection. This is apparent in the comparison of the amount of acetylcholine required to produce block when injected into the leg vein, which varies from 80 to 3000 gamma, while doses from 20 to 80 gamma will produce block if given via the

*The possibility exists that an increase in coronary flow during the hypoxemic period resulting in an increased delivery of acetylcholine-laden blood to the pacemakers might simulate an increased sensitivity. The reversal of the effect during the reoxygenation period would, however, appear to exclude this possibility since it has been shown[7] that after a period of hypoxemia a reactive hyperemia occurs during which blood flow through the coronary vessels is markedly increased. Despite this increase in coronary flow during the reoxygenation period, the sensitivity of the pacemakers returns to normal. It would therefore appear that the increased sensitivity seen in hypoxemia cannot be attributed to an increase in coronary flow.

catheter directly to the region of origin of the coronary vessels.

These experiments show that acute hypoxemia leads to progressive depression of the supraventricular pacemakers and conduction pathways of the heart. This effect is produced through a combination of a central and a peripheral mechanism. The central nervous mechanism probably involves stimulation of the vagal centers. The peripheral action as seen in the progressive increase in acetylcholine sensitivity probably occurs at the vagal terminations. This effect may be due to a direct inhibition of choline esterase or possibly due to the reported anti-choline esterase effect of epinephrine which apparently accumulates in the blood in severe hypoxemia. In addition, the inhibition of epinephrine action during severe hypoxemia would eliminate the stimulating effect of this substance on the supraventricular pacemakers.

These results emphasize that severe hypoxemia produces progressive heart block and even heart standstill, especially after the administration of vagotonic drugs.

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Infarction of The Right Ventricle Caused by Multiple Coronary Vein Ligation

By Ferdinand F. McAllister, M.D., and David S. Leighninger, M.D.

Ligation of the coronary sinus and all the visible anterior cardiac veins led to death in 5 out of 24 dogs. In 15 out of 17 of these dogs coming to autopsy, varying degrees of infarction of the right ventricle were found. The work emphasizes the importance of the superficial venous system in the drainage of the myocardium and reveals the inadequacy of the intramural system when the latter is forced to assume the entire outflow load.

DURING the course of studies on the revascularization of the heart, it was found that infarction of the right ventricle might be produced by occlusion of the coronary sinus and the anterior cardiac veins. Apparently the intramural venous drainage system cannot accommodate the entire arterial inflow rapidly enough to prevent myocardial damage.

In general, the blood supplied to the heart substance is drained by superficial veins and by intramural vessels. The superficial channels consist of the coronary sinus system and the anterior cardiac veins. The coronary sinus is located on the posterior aspect of the heart in the groove between the left auricle and the left ventricle and empties into the right auricle close to the ostium of the inferior vena cava. The coronary sinus has a rich network of tributaries and probably accounts for over 60 per cent of the coronary outflow. The anterior cardiac veins (fig. 1) lie on the anterior surface of the heart where they arise from the wall of the right ventricle and drain directly into the right auricle near the auriculoventricular junction. The intramural vessels drain into the various heart chambers and consist of the thebesian veins, the arterioluminal vessels, and the myocardial sinusoids. The intricate anatomic arrangement of these latter vessels has been described by Wearn and his associates.[1]

In an effort to protect the heart against coronary artery occlusion, Beck and his associates[2, 3] have recently introduced the use of a vein graft to convey oxygenated blood from the aorta to the coronary sinus. If the coronary sinus has been ligated close to its ostium in the right auricle, the establishment of such a graft reverses the blood flow in the coronary sinus and the latter functions as an artery. That this is beneficial has already been demonstrated. However, it has been postulated that an arteriovenous fistula effect might be produced in the heart substance because of the many free connections between the radicals of the coronary sinus and the anterior cardiac veins (fig. 1). The development of such connections would mean that increasing quantities of arterial blood entering the coronary sinus would be shunted through these superficial veins directly into the right auricle without benefit to the myocardium. In order to anticipate this possibility, a series of 24 dogs was prepared in which, as a preliminary operation, the coronary sinus and all the larger anterior cardiac veins were ligated. The latter were tied as near as possible to their ostia in the right auricle, care being taken not to include any arterial branches in the ligatures. Eight to twelve days later the surviving dogs were subjected to a second operation wherein a vein graft was inserted between the aorta and the coronary sinus. Seventeen of these dogs were examined post mortem one to forty-nine days following the initial

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operation. These dogs constitute the subject of this report. Five of the 17 dogs had only the initial operation, while 12 underwent the additional vein graft operation. Inasmuch as the serious effects of the preliminary procedure were not at first apparent and were not the prime objects of our investigations, many interesting data, such as electrocardiograms and venous and arterial pressures, were not obtained.

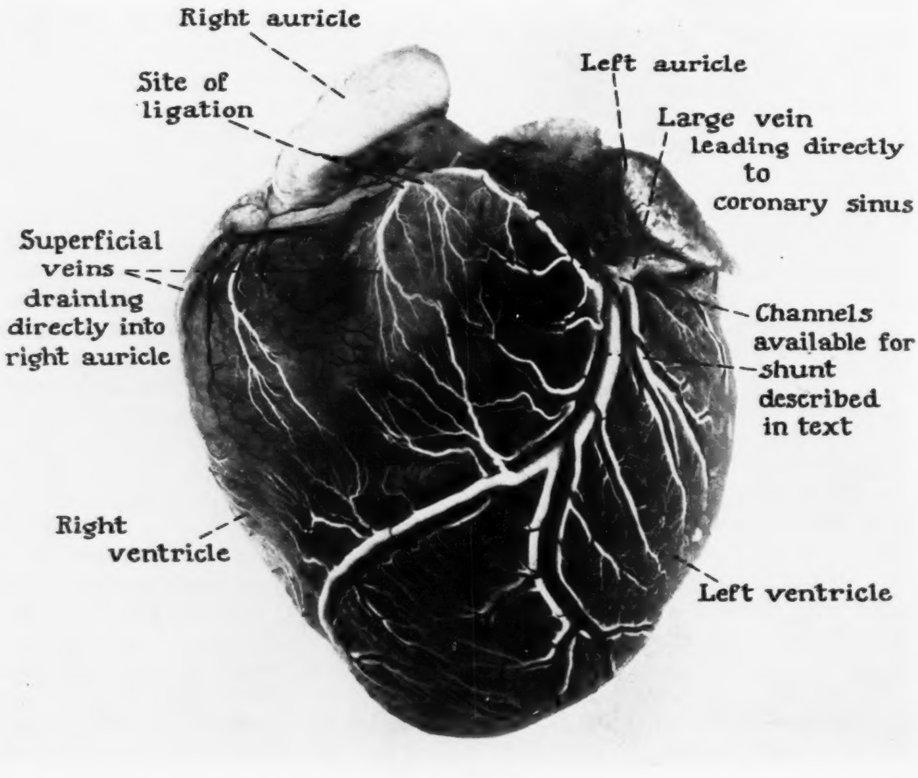

Fig. 1.—Photograph of a cleared dog heart. The arteries have been injected with black dye and the veins with white. On the surface of the right ventricle the superficial veins which drain directly into the right auricle may be readily seen.

Results

One of the striking clinical results of ligating both the coronary sinus and the anterior cardiac veins was the prostrating effect upon the dogs. In contrast to simple ligation of the coronary sinus which causes relatively slight postoperative disability, these animals remained sedentary for from four to nine days or longer. All seemed disinterested in their surroundings and the majority refused to eat for several days. Some were dyspneic at rest and developed a peculiar hacking cough.

The postoperative mortality was 12.5 per cent, more than double that for ligation of the coronary sinus alone. Since 2 dogs not included in this figure were sacrificed because of extreme illness and imminent death, the actual mortality is probably much higher. On the other hand, in a recent series of 96 dogs subjected to coronary sinus ligation alone, the postoperative mortality was 4.2 per cent. While the present

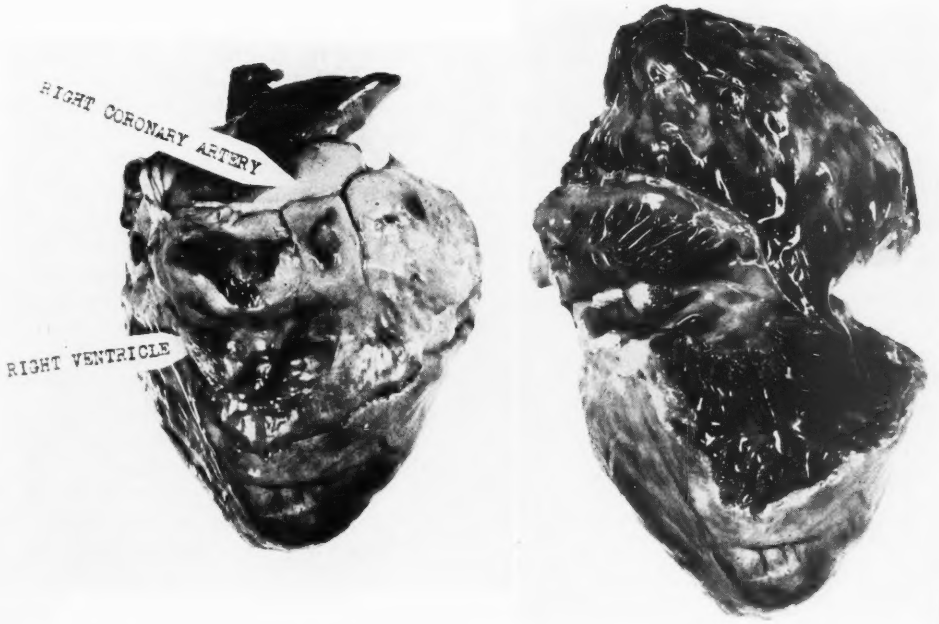

FIG. 2.—Gross appearance of a dog heart which has been subjected to ligation of the coronary sinus together with ligation of the superficial veins draining into the right auricle. *A* (Left). Dog 252. Autopsy performed 49 days following operation. The surface of the right ventricle shows extensive scarring. The right coronary artery has been opened and the major branches are patent. *B* (Right), Same specimen with the right ventricle opened and the wall turned back to show the endocardium. Note the numerous patches of scar.

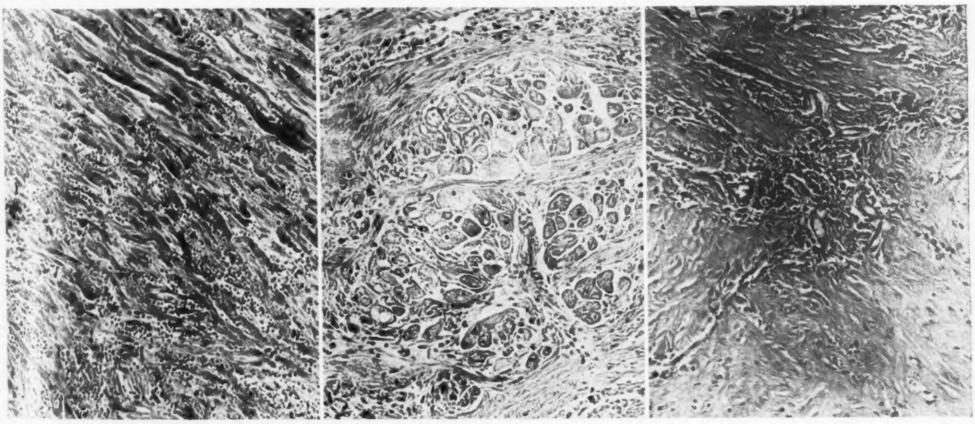

FIG. 3.—Photomicrographs of infarcted areas of the right ventricle. *A* (Left), Section from Dog 237 made ten days postoperatively. The muscle fibers have been split apart by edema fluid and extravasated red blood cells. *B* (Middle), Section from Dog 271 made twenty-three days postoperatively. There is necrosis of muscle cells with swelling, granulation, and vacuolation. There is round cell infiltration and fibrosis. *C* (Right), Section from Dog 252 made forty-nine days postoperatively. There is phagocytosis of hemosiderin, advanced fibrosis, and complete muscle replacement.

TABLE 1.—*Gross Findings and Duration of Process*

Dog No.	No. Days after First Operation that Autopsy Was Performed	Gross Findings
258	1	Marked hemorrhagic engorgement of right ventricular wall
209	3	Heart dilated. Hemorrhagic engorgement, right ventricle
269	7	Hemorrhagic necrosis of right ventricular wall with thinning and mural thrombus. Advanced congestion throughout both lung fields but no emboli found
309	7	Marked hemorrhagic engorgement of right ventricular wall
237	10	Extensive hemorrhagic necrosis of right ventricular wall. Latter thin and devoid of muscle. Mural thrombus. Massive bilateral pulmonary infarction with pulmonary emboli
271	23	(Cardiac decompensation following op.) Fibrotic, thinned right ventricle with dense plaque of scar in infundibulum
256	24	Moderate thinning and fibrosis, right ventricle
270	31	Advanced fibrosis and muscle replacement in a wide zone of the right ventricle along the interventricular groove
259	37	Some fibrosis. Large vein entering floor of sinus found open
261	37	No damage to right ventricle. Large vein entering floor of sinus found open
260	40	Slight, patchy fibrosis of right ventricle
272	41	Small patches of fibrosis in the infundibulum of the right ventricle
262	42	Marked fibrosis of right ventricle with areas of complete muscle replacement
255	43	No damage to right ventricle. Large vein entering floor of sinus found open
254	44	Thinning, patchy fibrosis and much muscle replacement
251	45	Slight thinning and fibrosis, right ventricle
252	49	Markedly thinned and fibrotic right ventricle

series is perhaps too small to yield a statistically significant mortality rate, nevertheless, the above-mentioned elevated mortality figure of 12.5 per cent is in keeping with the clinical course and the pathologic findings to be described below.

Of the 17 dogs studied by postmortem examination, 15 showed a varying degree of disease of the right ventricle. This ranged from thinning and patchy fibrosis to extensive infarction. An example of moderately severe scarring may be seen in figure 2. The most striking damage to the right ventricle was usually seen in that portion which is normally the thinnest near the interventricular groove and particularly in the infundibulum. Early changes were those of edema, subendocardial and subepicardial hemorrhage, and hemorrhagic necrosis. Later changes consisted of muscle replacement, atrophy, hemosiderosis, and fibrosis (fig. 3). Table 1 describes the gross findings in each case and the duration of the process.

The 2 dogs which were sacrificed at seven and ten days respectively because of extreme illness are of especial interest. Both showed massive infarction of the right ventricle with mural thrombi and extensive hemorrhage into the lungs. In one of these there were bilateral pulmonary infarcts involving complete lobes and molded emboli almost occluding the main branches of the pulmonary artery. Another animal is of considerable interest in that it was explored at ten days and found to be in frank decompensation with a greatly dilated, laboring, cyanotic heart and pericardial effusion and bilateral hydrothorax.

In those specimens showing severe disease, the right coronary artery was dissected out with its radicals or injected with dye in order to determine whether or not any significant arterial branches had been included in the ligatures placed about the veins. Although a few tiny arterial twigs had been thus ligated, no instance of occlusion of a significant arterial branch was found.

Microscopic sections taken through the diseased areas of the right ventricle (fig. 3) show variable pictures depending upon the duration of the process. In the early period there is engorgement of the tissue with edema fluid and extravasated red blood cells. The muscle bundles become split apart and the cells become

swollen. Later specimens show the cytoplasm to become pale, vacuolated, and granular. Macrophages appear and contain ingested hemosiderin together with fragments of cellular debris. The muscle bundles disintegrate and young fibroblasts grow in to replace them. As the process advances, the ventricular wall becomes thinner and, in the late specimens, is represented almost entirely by connective tissue.

Discussion

Naturally, one would wonder what role the second operation has played in the production of this pathologic picture. It is probable that it has had very little to do with the damage to the right ventricle since some of those animals sustaining the most severe myocardial injury were not subjected to the second operation. Furthermore, extensive damage to the

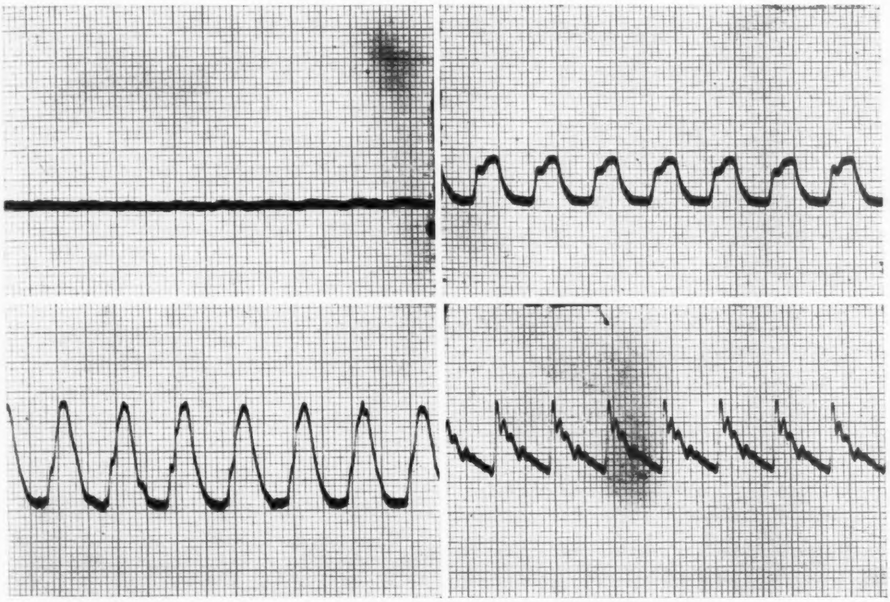

FIG. 4.—Changes in coronary sinus pressure associated with ligation. (Records made with Sanborn Electromanometer.) *A* (Upper left), Tracing made from the coronary sinus of a normal dog under ether anesthesia. Pressure 0–4 mm. mercury. *B* (Upper right), Tracing made from the coronary sinus of the same dog five minutes after ligation of the sinus at its ostium. Pressure 55/15 mm. mercury. *C* (Lower left), Tracing made two hours after sinus ligation. Pressure 95/15 mm. mercury. *D* (Lower right), Tracing made from the thoracic aorta two hours after sinus ligation. Pressure 95/50 mm. mercury.

Two of the 17 dogs showed normal-appearing myocardium in the right ventricles. In these 2 animals, a large vein was found buried in the epicardial fat, freely communicating with the right ventricle and draining into the floor of the sinus just at the ostium. In this hidden position, it was missed at operation and escaped inclusion in the coronary sinus ligature. In one other dog showing a very mild degree of fibrosis there was an open vein in this location.

right ventricle is not seen in dogs that have been subjected to exactly the same procedures as this present group with the single exception that the anterior cardiac veins have not been ligated.

What is the mechanism responsible for producing infarction in this group? To answer this question requires further study, but one may reason as follows: Gregg and Dewald[4] have shown that the intravenous pressure in a coro-

nary vein or in the coronary sinus rises after ligation of the coronary sinus to values approaching the aortic systolic pressure during systole and to 20 to 40 mm. Hg during diastole. Some idea of the extent of these changes may be obtained from the pressure tracings in figure 4 taken from the coronary sinus before and after ligation of the latter. The ligation of the additional superficial veins draining the right ventricle puts the entire load for venous drainage from that chamber on the thebesian and arterioluminal vessels. The "run off" into the latter is inadequate and, with pressure in the capillaries and veins approaching aortic levels, blood and edema fluid extravasate into the interstitial spaces. The thin-walled right ventricle can ill accept such engorgement. Furthermore, it has been our observation that the radicals of the right coronary artery of the dog are of very small caliber and the flow through these radicals is probably reduced not only by the greatly elevated intraluminal peripheral resistance but also by extraluminal compression from distention of the myocardium. The net result of these forces is a markedly diminished or absent flow of oxygenated blood through the right ventricle. With the passage of time, compensation eventually occurs, but not before there has been considerable destruction of ventricular muscle.

That the effect is largely one of venous occlusion and not reduction in available channels for arterial inflow may be deduced from the fact that by inadvertently leaving one moderate-sized superficial vein free to drain into the right auricle, the right ventricle was spared in two dogs and only slightly damaged in a third.

These observations are in agreement with those of Gregg and Shipley[5] on superficial cardiac vein occlusion and lend support to their view that the thebesian vessels are not, in themselves, sufficient for adequate drainage of all the blood from the myocardium.

The value of these observations is twofold. In the first place, the discovery of the destructive effect on the right ventricle instituted by ligating both the coronary sinus and the anterior cardiac veins should eliminate this procedure as a method of preventing an arteriovenous fistula effect in the Beck operation. Unless some other technic can be devised, it would be preferable to accept the risk of any arteriovenous fistula which might develop. In the second place, a method has presented itself whereby acute and chronic disease of the right ventricle may be produced for experimental study.

Summary and Conclusions

1. Twenty-four dogs were subjected to ligation of the coronary sinus together with ligation of the anterior cardiac veins. This was found to be a prostrating operation and carried a mortality of over 12.5 per cent.

2. Seventeen of the dogs were studied post mortem one to forty-nine days postoperatively. Twelve of the 17 dogs had sustained a second operation consisting of a vein graft connecting the aorta with the coronary sinus. Reasons are given why it is felt that this second procedure was not instrumental in producing the pathologic picture presented.

3. Fifteen of the 17 dogs showed damage to the right ventricle, varying from thinning and patchy fibrosis to massive infarction. The microscopic sections resembled various stages of infarction.

4. Two dogs showing no damage to the right ventricle were found to have one large patent vein opening into the floor of the coronary sinus at its ostium.

5. The following conclusions are drawn:

a. Ligation of the coronary sinus and the anterior cardiac veins alone produces infarction of the right ventricle by raising the intraluminal pressure to such an extent that, together with extraluminal compression from edema fluid, there is inadequate flow of oxygenated blood.

b. The intramural venous drainage system is incapable of assuming the entire venous outflow load.

c. Ligation of the anterior cardiac veins should not be used to prevent the development of an arteriovenous fistula effect in the Beck operation.

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The Question of the Function of the Right Ventricular Myocardium: An Experimental Study

By Augustus C. P. Bakos, M.D.

A laboratory study designed to investigate the independent pump-like function of the right ventricle of the dog heart is presented. Systolic and diastolic pulmonary arterial pressure fluctuations were used as the definitive criterion for pumping efficiency. Control pressure levels are compared with those recorded after complete damage, by electrosurgical coagulation, of the free right ventricular myocardium. The degree of damage so produced was ascertained from an analysis of electrocardiographic, physiologic and histologic observations. The results are discussed and explained in terms of a postulated mechanism based upon the architecture of the individual ventricular muscle bands.

THE MUSCULATURE of the right ventricle of the normal mammalian heart is generally considered to function as an efficient pump, alternately contracting and relaxing and thus transferring blood from the venous side of the systemic circulation to the pulmonary arterial side. This, supposedly, lowers pressures in the systemic veins and raises them in the pulmonary arterial circulation and assures an adequate pressure gradient for normal blood flow in both systems.[1-4] On the basis of this concept it is reasonable to assume that a rise in the upstream (peripheral venous) and a fall in the downstream (pulmonary arterial) pressures will occur as a result of a decrease in the pumping efficiency of this chamber. The usual elevation in the peripheral venous pressure in clinical cases of dissociated right-sided heart failure is generally interpreted as a manifestation of such a unilateral deficiency.[5-11] Much clinical[12-14] and experimental[15-18] evidence has accumulated in the past, however, which conflicts with this concept. Starr[15] demonstrated that experimentally produced severe damage of the right ventricle of the dog heart did not effect more than a minimal rise in the upstream systemic venous pressure. This latter investigation gave impetus to the present studies which are concerned with the effect of similarly produced damage of the right ventricle on the downstream systolic and diastolic pressures in the pulmonary artery. These experiments demonstrate a maintenance of the control level of both these pressures as well as the systemic venous pressure after the production of complete coagulation and necrosis of the myocardium of this chamber. This seems to indicate that active contractions of the right ventricular myocardium of the dog heart are not absolutely necessary for efficient force-pump function of the right ventricle. An explanatory anatomic and physiologic correlative study is discussed.

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A preliminary report of this study was presented at the annual meetings of the Federation of American Societies for Experimental Biology, March, 1948. (Federation Proc. 7: 204, 1948.)

Methods

Acute experiments were performed on healthy mongrel dogs anesthetized by an initial injection of 35 mg. per kilogram of body weight of sodium pentobarbital (Nembutal) and then placed in a supine position. With the attainment of surgical anesthesia the thorax was opened by a longitudinal, midsternal incision; thereafter the animals were sustained by intermittent positive pressure from an artificial respirator. A hammock-like sling was devised from the pericardial sac as a means of preventing positional changes of the heart during the course of the experiments. Mean systemic arterial pressure was recorded by a mercury manometer from a direct cannulation of the left carotid artery. A membrane manometer of the Hürthle type was employed for the determination of the systolic and diastolic pressure fluctuations in the pulmonary arterial system. This was accomplished by the in-

sertion of a glass cannula into a stem branch of the left pulmonary artery. Heparin was used as the anticoagulant. Peripheral venous pressures were obtained by periodic observations of the meniscus of a saline hydrostatic manometer connected to the femoral vein. The arterial pressures were recorded continuously on smoked paper. The "zero" pressure of all systems was referred to the horizontal level at which the superior vena cava entered the right atrium.

After the allowance of a sufficient period of time for the animals to recuperate from the preliminary operative procedures, cauterizing instruments were periodically applied to the right ventricular musculature. Short intervals of time were permitted between applications for cardiovascular readjustments. In early experiments a soldering iron was used as the cauterizing agent and many repeated applications were necessary to produce extensive damage. In subsequent studies a high-frequency electrosurgical coagulator was resorted to in order to produce more severe and practically complete anatomic damage of the musculature. With the use of this latter method, which required fewer applications, it was necessary to exercise great care in order to prevent immediate and fatal ventricular fibrillation. This was accomplished by removing the electrocoagulator at the first indication of any irregularities in rhythm. Cauterization was produced in all experiments by a direct application of the cautery to the whole epicardial surface of the right ventricle; charring was restricted to the surface landmarks of the ventricle as determined by preliminary anatomic studies of normal dog hearts. Damage was inflicted to the maximum degree that could be obtained by the particular method used. With the use of the soldering iron this was determined by the seepage of luminal blood through small fissures occurring in the charred muscle; with the electrocoagulator a definite period of time, as determined by preliminary studies, was allowed for each cauterization in order to produce destruction of the entire thickness of the wall. It was necessary to raise the heart momentarily in order to reach its posterior portions with the cautery instruments.

In several experiments the right coronary artery was dissected free from its supporting tissues and ligated near its aortic origin. Damage was then inflicted to the right ventricle of the 2 animals that survived this procedure. In two other experiments superficial damage to the left ventricular muscle was produced subsequent to the production of maximum damage to the right side.

Unipolar electrocardiographic tracings, utilizing a nonpolarizing electrode,[19] were recorded directly from several selected points representing the whole area of the right ventricular epicardium. These were taken initially as controls and later, from the same selected points, in 7 animals after myocardial damage was completed by electrosurgical coagulation.

The degree of damage so produced in these studies was ascertained at the termination of each experiment by a gross and microscopic post-mortem examination. The development of any peripheral or pulmonary venous congestion was also noted at this time.

Observations

The following results are based on observations taken from the 21 experimental animals which survived the drastic procedures employed. In 9 animals the soldering iron was used, in 10 the electrosurgical coagulator, and in 2 a ligation of the right coronary artery followed by electrosurgical coagulation. In all these right ventricular damage was carried out to the maximum degree.

In all twenty-one experiments the systolic and diastolic pressures in the pulmonary artery remained surprisingly constant from the initial control period to the time following the completion of the damage. As can be seen in figure 1, which is a tracing from a representative experiment, these pressures fluctuated between approximately 40 mm. Hg systolic and approximately 10 mm. Hg diastolic initially as well as after the final charring period. These values are closely similar to those obtained in all animals studied and are consistent with the results reported by others.[20-22] In some instances the animals were allowed to survive as long as six hours after maximum right ventricular damage without any recorded change in these pressures. Following this extensive damage the peripheral venous pressure did not show more than a 1 or 2 cm. of water rise or fall in any experiments. This corroborated Starr's[15] previous observations. No significant changes were observed to have occurred in the level of the mean systemic arterial pressures. A small drop in these latter pressures usually occurred following the cannulations and the chest surgery; however, a steady state was reached prior to the infliction of damage to the heart and from then on no change was noted.

It was further noted that following this extensive destruction of the musculature of the right ventricle the free wall of this chamber failed to show any signs of active contractions. This occurred without any evidence of altera-

tion in the systolic or diastolic pulmonary arterial pressures.

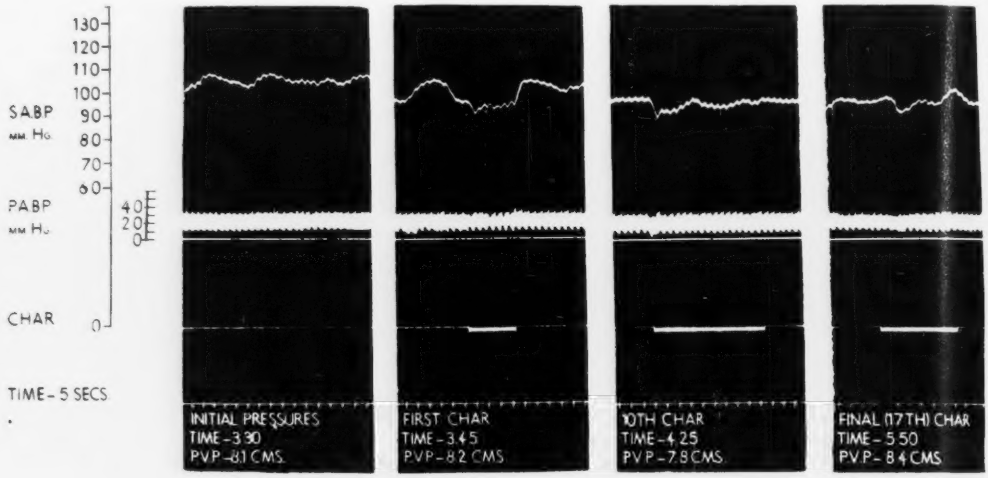

FIG. 1.—The effects of charring of the right ventricular myocardium on the systemic arterial blood pressure (S.A.B.P.—upper tracing) and the pulmonary arterial blood pressure (P.A.B.P.—lower tracing). Each arterial system is referred to its respective "zero" pressure level. Peripheral venous pressures (P.V.P.) observed during these periods are numerically indicated below in centimeters of water. (Dog 16)

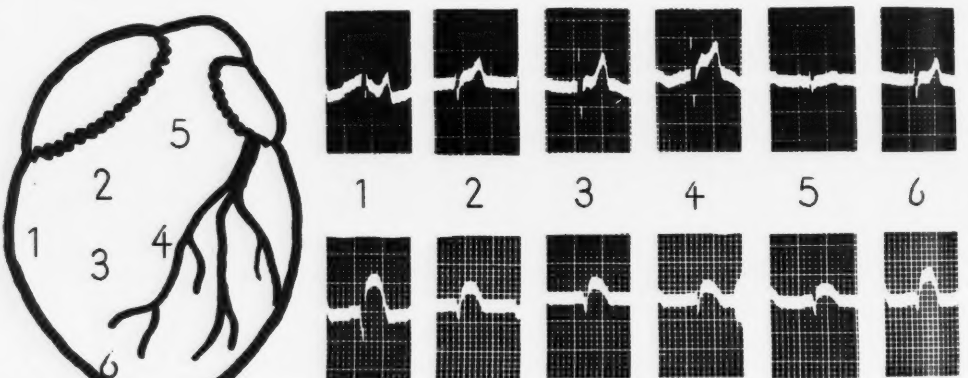

FIG. 2.—A comparison of direct unipolar electrocardiographic tracings recorded from selected points during the control period (upper series) with those recorded from these same points following electrosurgical damage of the right ventricle (lower series). The numbers refer to the points on the epicardial surface of the right ventricle from which these tracings were obtained. (Dog 12.)

The only significant changes in pressures were observed in the two experiments in which the left ventricle was moderately damaged subsequent to maximum destruction of the right. In these instances, and after a few cauterizations of the epicardium of the left ventricle the pressures in both the pulmonary and systemic arteries began to fall simultaneously

and finally, with the death of the animal a few minutes later, they reached the static level.

Electrocardiographic tracings recorded directly from the epicardial surface of the normal right ventricle by means of a nonpolarizing unipolar exploring electrode displayed ventricular complexes of the type reported by Wilson and his associates.[19] These showed the same variations in form as was to be expected from points from the various regions of the epicardial surface of the right ventricle from which they were obtained. In general they all showed characteristic R- and S-wave deflections, isoelectric RS-T segments, and upright T waves (fig. 2, upper series). Following the production of maximum damage to the right ventricle these same selected points produced ventricular complexes of radically different

FIG. 3.—Anterior view of dog's heart demonstrating effect of multiple applications of the soldering iron to the right ventricular myocardium.

outline but which closely resembled each other regardless of the position of the exploring electrode (fig. 2, lower series). These were characterized by deep QS deflections, representing the potential variations of the cavity of the right ventricle, and upwardly convex and upwardly displaced RS-T segments. This latter change, in all probability, had its origin from the zone lying between the destroyed muscle of the wall of the right ventricle and the normal undamaged left ventricle.

Gross and microscopic postmortem examinations showed that over 75 per cent necrosis of the wall of the right ventricle was produced in experiments in which the soldering iron was used as the cauterizing agent (fig. 3). With the use of the electrosurgical coagulator these studies demonstrated coagulation necrosis of the entire area and thickness of the wall of the right ventricle including the subendocardial myocardium so that the free wall of the right ventricle showed complete anatomic damage. No evidence of peripheral venous or pulmonary congestion or edema was noted at this time in any of the experiments including the ones in which the left ventricle was damaged subsequent to the right. In these latter experiments postmortem observations revealed small circumscribed areas of necrosis of the free wall of the left ventricle due to the few applications of the cautery prior to death of the animal.

Discussion

It can be stated without equivocation that as a result of the cauterization procedures employed in these acute experiments the right ventricular myocardium was thoroughly damaged anatomically, and no longer functioned as an actively contracting organ. This is apparent from the postmortem gross and microscopic findings of coagulation necrosis of the entire free wall of the right ventricle and the conspicuous absence of action potentials (electrocardiographic R waves) which normally originate from activity of the right ventricular myocardium.

Before discussing the results of these experiments in terms of function of the right ventricle the value of systolic and diastolic pulmonary arterial pressure changes as an index of the efficiency of the right ventricular pump must be considered. It is well known that the hemodynamics of a pulsating circulation system depends upon the discharge volume of the pump (stroke output), and upon the elasticity, and peripheral resistance of the receiving conduits and upon the viscosity and volume of the circulating fluid. Changes in any of these factors can alter the size and configuration of the pulse pressure curves recorded. The stroke output of the pump, of course, is directly dependent upon the amount of fluid it receives and the efficiency of its forcepump-like contractions. The manner in which these factors affect the systolic and diastolic arterial pressure fluctuations is adequately discussed in textbooks of physiology. It is important to state here, however, that with a decrease in pump stroke output (other factors remaining constant) there would result a greater drop in the systolic pressure than in the diastolic pressure. The net effect would be a decrease in the pulse pressure. The reason for this less pronounced effect on the diastolic pressure is that as a result of the lower pressure at the end of the systolic ejection period (owing to the decreased stroke output) the pressure gradient is less throughout diastole and therefore less blood will "run off" through the peripheral arterioles. If the heart, which is the source of the energy driving the fluid through the system, should entirely cease its function as a contracting pump organ, its *stroke* output will be reduced to zero and the pressures in the receiving arterial system will then be dependent upon but *less* than the head of pressure in the *upstream* peripheral veins.

This line of reasoning can now be applied, along with a consideration of the other hydrodynamic factors, to the right ventricular pump and the pressure fluctuations in the pulmonary arterial system. Normally, since the *right* atrial pressures are *lower* than those recorded in the pulmonary arteries, it is obvious that the vis a tergo of the *left* ventricular pump, along with the intrapleural respiratory pressure changes and the skeletal muscle "squeeze," cannot be responsible for the *higher* pulmonary arterial pressures. Because of the decreasing pressure gradient from the *right ventricle* to

the *left atrium*, the pulmonary arterial pressure must therefore be dependent upon pressure changes occurring in the cavity of the right ventricle. According to our classic concepts the independent active pumping contractions of the right ventricle are entirely responsible for these intracavity pressure changes which thus in turn maintain the stroke output into the pulmonary arterial system. The pressure fluctuations in this system vary as the product of the stroke output of the right ventricle and the peripheral resistance offered by the pulmonary arterioles. Increases in the latter can no doubt compensate for minor decreases in the stroke output and still maintain an adequate mean pressure level. Under these conditions, however, the pulse pressure will decrease and with eventual reductions of the right ventricular stroke output to zero, the pulsatile flow will cease altogether and the pulmonary arterial pressures will then be dependent upon the level of the filling pressure in the upstream peripheral veins. Likewise, regardless of the high degree of elasticity possessed by the pulmonary arterial conduits (which thus affords relatively large stroke volume changes with minor pressure changes) the *ultimate* pulse pressure will be directly dependent upon the stroke volume of the right ventricle.

In so far as no recordable changes were observed to occur in the systolic, diastolic, or pulse pressures in the pulmonary arterial system following the production of this extreme degree of right ventricular damage, the question is raised as to the source of energy responsible for the output of the right ventricle and the maintenance of these pressures. The artificial respirator used in these studies was not the source, since the pulmonary arterial pressure fluctuations were not synchronous with the rhythm of the respirator. It was further observed that when the respiratory pump was momentarily turned off the pressure fluctuations in the pulmonary arteries continued. The relatively constant systemic venous pressure, which was well below the recorded pulmonary arterial pressure in all experiments, excludes the possibility that the latter pressures were maintained by the vis a tergo of the left ventricular myocardium and the other factors which tend to maintain the systemic venous pressure.

The results observed in the two experiments in which the left ventricle was superficially cauterized subsequent to maximum damage of the right ventricle seem to indicate that the energy expenditure of the contracting left ventricle is directly responsible for the maintenance of these pulmonary arterial pressures. The basis for a probable explanation of the manner in which this occurs can be seen from a study of the architecture and function of the four main, distinct, and independently contracting ventricular muscle bands comprising musculature common to both ventricles. The structural relationships between these muscle bands are similar in both human and canine hearts.[23-25] These include the superficial sinospiral and bulbospiral muscles (fig. 4) and the deep bulbospiral and sinospiral muscles (fig. 5). Each of the superficial muscles partially encircles both ventricles, but considered together they completely envelop, in a supplementary manner, the whole surface of the heart. The deep sinospiral completely encircles both ventricles but splits, at the posterior interventricular groove, in such a manner that the greater mass of its fibers, though continuous with the rest of the muscle, projects deeply and enters into the formation of the interventricular septum. The lesser mass of this muscle passes more superficially and fuses with the previously described superficial muscles. The deep bulbospiral is the only muscle band which is confined to one ventricle, namely, the left. It has been postulated by Robb and Robb[25] that this muscle band is important, owing to its sphincteric arrangement around the base of the left ventricle, in completing ventricular ejection and maintaining systolic pressures in the aorta by supporting the column of blood ejected. These same investigators state that "the deep sinospiral muscle forms the main mass of the right ventricle and must be responsible for the maintenance of the pulmonary circulation."

The importance of these muscle masses as a probable explanation for the results of these experiments is based upon (1) their encircling

arrangement—enveloping both ventricles in one continuous sweep—and (2) the fact that the *portion* of these muscles making up the left ventricle is larger, thicker, and more powerful in its contraction than the *portion* making up the thinner right ventricle. Because of this encircling arrangement the tension developed during contraction of the undamaged, thicker, portion is mechanically transmitted, through this anatomic continuity, to the damaged, nonfunctioning, thinner, right ventricular portion. Since the mass of the left ventricular portion is far greater than that of the right ventricular portion it is *assumed* that the contribution of each towards the total tension developed during contraction of the muscles as a whole is also of this proportion. Thus, according to this postulation, removal of the thinner right ventricular contribution

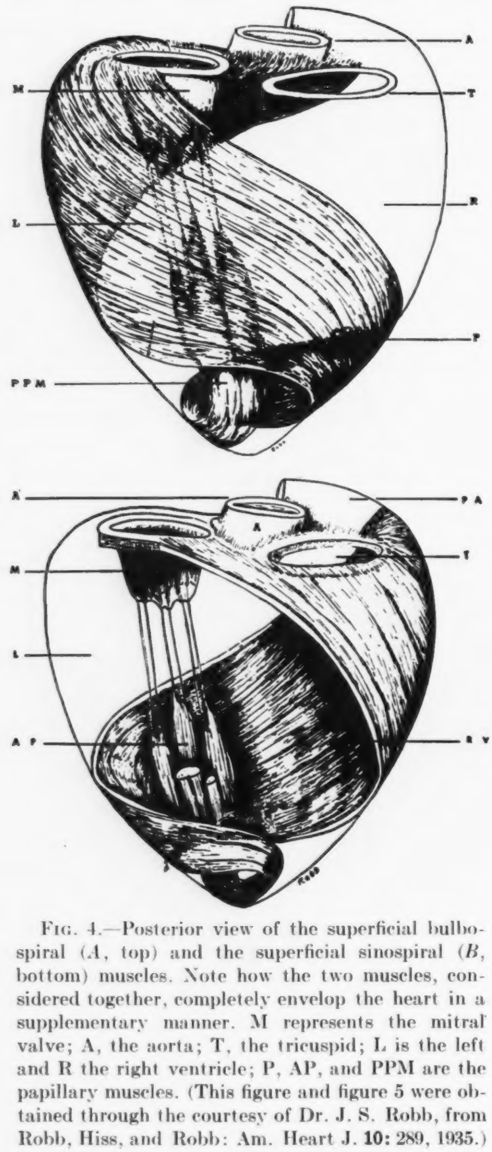

FIG. 4.—Posterior view of the superficial bulbospiral (*A*, top) and the superficial sinospiral (*B*, bottom) muscles. Note how the two muscles, considered together, completely envelop the heart in a supplementary manner. M represents the mitral valve; A, the aorta; T, the tricuspid; L is the left and R the right ventricle; P, AP, and PPM are the papillary muscles. (This figure and figure 5 were obtained through the courtesy of Dr. J. S. Robb, from Robb, Hiss, and Robb: Am. Heart J. **10:** 289, 1935.)

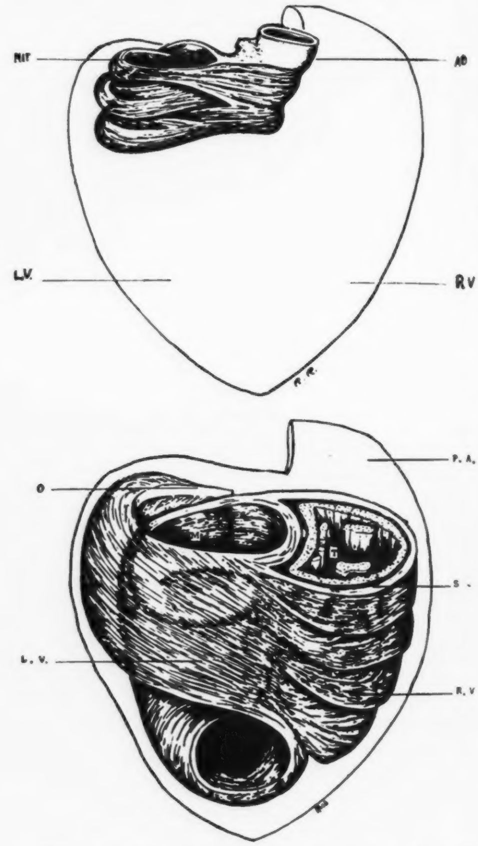

FIG. 5.—Posterior view of the deep bulbospiral (*A*, top) and the deep sinospiral (*B*, bottom) muscles. Note that the deep bulbospiral muscle is limited to the base of the left ventricle and that the deep sinospiral completely encircles both ventricles and also forms the muscular interventricular septum. Labels same as in figure 4.

does not materially subtract from the *total* tension developed during systole. Therefore, contraction of the left ventricular portion transmits tension to the right ventricular portion with a resultant increase in the cavity pressure of this latter chamber and consequent ejection of blood into the pulmonary arterial system. When the thicker, more powerfully contracting, left ventricular portion is damaged, subsequent to maximum damage of the right ventricular portion, the ejection of blood from both chambers decreases with a resultant simultaneous drop in the pressures in both arterial systems.

Summary and Conclusions

In acute experiments performed on 21 dogs the musculature of the right ventricle was directly and completely damaged by cauterizing instruments. No changes were observed to occur in the peripheral venous and systolic and diastolic pulmonary arterial pressures following this degree of damage as compared to the control level of these pressures recorded prior to the cauterizations. The degree of damage produced was ascertained from direct unipolar electrocardiographic tracings recorded during the study and later by gross and microscopic postmortem observations.

Despite this complete inactivation of the right ventricle the myocardium of the left ventricle apparently mechanically transmitted its energy, through the continuity of the circumscribing individual ventricular muscle bands, to the right ventricle so that this latter chamber passively functioned as an efficient force pump.

An actively functioning right ventricle is therefore not absolutely necessary for the maintenance of a normal pressure gradient in the pulmonary arterial tree. It is also apparent that the function of the two ventricles cannot be dissociated in an independent manner since the architecture of the distinct myocardial bands makes it mandatory for an integrated and unified function of both chambers.

The relationship of these experiments to the dynamics of congestive heart failure is yet to be considered. Perhaps chronic experiments performed along similar lines may offer interesting observations towards the solution of this perplexing problem. Recent observations[14] during clinical investigative studies seem to parallel the conclusions from the observations in these present experiments.

Acknowledgments

The author wishes to express his appreciation to Dr. C. F. Morgan and Dr. I. Starr for their valuable criticisms and suggestions during this investigation.

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Anti-Adrenergic Effects of Nitroglycerin on the Heart

By W. Raab, M.D., and E. Lepeschkin, M.D.

The therapeutic effect of nitroglycerin is generally attributed to its coronary dilator effect alone. In contrast, it could be shown that nitroglycerin also counteracts the chronotropic as well as the electrocardiographic T-wave depressing effects of epinephrine, arterenol and cardiac sympathin upon the heart. Accordingly, its therapeutic action in angina pectoris is suspected as being largely due to a chemical protection of the heart muscle against the chemically anoxia-producing effects of sympathomimetic amines.

There is a widespread tendency among cardiologists to interpret the mechanism of functional cardiac changes primarily or exclusively in terms of alterations of the coronary blood flow or of cardiac muscular dynamics, while little or no attention is paid to the fundamental role of myocardial cell metabolism and its neurohormonal regulation. This tendency applies also to the evaluation of the effects of nitroglycerin, the coronary-dilator action of which is generally assumed to explain all of its cardiac manifestations and especially its therapeutic efficiency in angina pectoris.

However, some investigations, dealing with the chemically anoxia-producing effects of sympathomimetic neurohormones and their derivatives[1,15,16,24,26] and with the probable pathogenic role of epinephrine and sympathin in the origin of the anginal syndrome,[2] have made the purely mechanistic conception of the action of nitroglycerin on the heart questionable. They have put emphasis on the possibility that nitroglycerin might interfere with the oxygen-consuming, anoxia-producing effects of epinephrine-sympathin on the contractile substance of the heart directly, in a way similar to the direct counteraction exerted by nitroglycerin against the vasopressor effect of epinephrine on the contractile substance of the blood vessels.[3] A specific indication of such an antiadrenergic action of nitroglycerin on the heart was seen in the fact that the cardioaccelerator effects of epinephrine, of stimulation of the stellate ganglia, and of acetylcholine in the atropinized cat were markedly diminished in the presence of nitroglycerin.[4]

The following experiments were carried out in order to further elucidate the interference of nitroglycerin with adrenergic actions upon the heart.

Methods

Atropinized cats under Nembutal anesthesia, with the adrenal glands tied, and with artificial respiration, were used throughout. Rapid intravenous injections were given in an exposed femoral vein; slow infusions were made with a motor-driven syringe, operating at a constant velocity and connected with a femoral vein. The stellate ganglia were stimulated by means of attached shielded-wire electrodes and a "Variac" transformer at a voltage of 10. The blood pressure was recorded from a common carotid artery. Electrocardiograms were synchronized with corresponding points of the blood pressure curve through a time marker on the kymograph which was connected with the switch of the electrocardiograph. In most instances chest leads CR_1 and CR_4 were used, as they were found to be least influenced by the position of the heart. In a few experiments extremity leads and leads from the pericardial surface were registered. The changes of the amplitude of the T waves above and below the zero line were plotted on graph paper together with the blood pressure and heart rate curves. Because of the frequent absence of a distinct T-P segment, caused by a fusion of the T and P wave because of tachycardia, the P-R junction was considered the most reliable representation of the zero line.

Epinephrine and dl-arterenol* (nor-epinephrine,

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*We wish to express our appreciation to Dr. M. L. Tainter of the Sterling-Winthrop Research Institute, Rensselaer, N. Y., through whom dl-arterenol was generously supplied.

supposedly identical with sympathin[5-7]) and sympathin, extracted from cattle hearts, were injected rapidly (two seconds) in doses of 5 to 40 γ in 4 to 6 cc. of Ringer solution or infused slowly at a speed of 1.0 cc. per minute (each cc. contained 50 γ).

Cardiac sympathin was obtained through extraction from fresh cattle heart by a slight modification[11] of the method of von Euler.[8] The dosage was established through colorimetric assay of the fresh extracts by the method of Shaw[9] as modified by one of us.[10] It was expressed in "γ equivalents," each of which corresponded to the colorimetric and approximately to the vasopressor effect of 1 γ of epinephrine.[11] Immediately before injection the acid extracts were brought to a pH of 7 with sodium bicarbonate.

Nitroglycerin was injected or infused intravenously before or together with the other substances and procedures in doses of 2.0 to 10.0 milligrams.

Results

Epinephrine, Arterenol (Synthetic Sympathin), and Nitroglycerin. Injections of epinephrine and of arterenol were followed by elevations of the blood pressure (70 to 125 mm. Hg) which were of about the same magnitude with both substances; the injections were also followed by cardiac acceleration (10 to 92 beats per minute) which was practically the same for both substances, and by electrocardiographic manifestations almost identical for both drugs. The electrocardiographic findings consisted essentially of a transient flattening or inversion of the T wave between the 15th and 50th to 150th second and usually a subsequent elevation of the T wave, lasting until about the 200th second (fig. 1). (In most instances there was an early elevation of the T wave, beginning two to six seconds after injection and lasting for only a few seconds. This phenomenon, which was also present on injection of corresponding amounts of plain Ringer solution, is apparently due to cooling of the subendocardial ventricular muscle layers and is not specific for the sympathomimetic amines used.)

Injection of nitroglycerin alone for control purposes was followed by a transient fall of the blood pressure (30 to 60 mm.), usually a slight cardiac acceleration but, in some instances, a very slight retardation, and a minimal to moderate elevation of the T wave, persisting from a few seconds to about two hundred seconds.

When epinephrine or arterenol was injected or infused simultaneously with nitroglycerin, the blood pressure elevation was weakened or transformed into a fall, the cardiac acceleration was diminished or abolished, epinephrine-induced extrasystoles did not recur, and the adrenergic depression of the T wave was weakened (decreased or shortened or both) or entirely abolished (figs. 1 and 2), even if the elevations of the T wave, due to nitroglycerin itself, were taken into consideration (table 1). The succeeding elevation of the T wave, which is probably caused by a transient hyperpotassemia,[12] was not significantly altered. Changing the sequence of nitroglycerin control injections and combined nitroglycerin-epinephrine or arterenol injections did not affect the results.

Faradic Stimulation of Stellate Ganglia and Nitroglycerin. Stimulation of the stellate ganglia (both sides simultaneously or the right side alone for ten to thirty seconds) was followed by cardiac acceleration (20 to 80 beats per minute) and by flattening or inversion of the T wave which persisted for one to four minutes (fig. 3). If the stimulation was repeated thirty to forty seconds after intravenous injection of nitroglycerin, at a time when the transient T-wave changes produced by nitroglycerin itself had disappeared, the electrocardiographic effect of the stimulation was diminished or abolished (table 1). No significant diminution of the average cardiac acceleration was observed, in contrast to earlier experiments[4] in which nitroglycerin had been infused simultaneously with the stimulation.

Injection of Cardiac Sympathin and Nitroglycerin. Except for a transient initial fall and a somewhat retarded maximal elevation of the blood pressure, the vasopressor, cardioacceleratory, and electrocardiographic effects of sympathin, extracted from the heart muscle of cattle, were in several experiments practically identical with those of colorimetrically equivalent doses (5 to 30 micrograms) of epinephrine or arterenol (fig. 4). Combined injection with nitroglycerin resulted in a weakening of the vasopressor, cardioaccelerator, and electro-

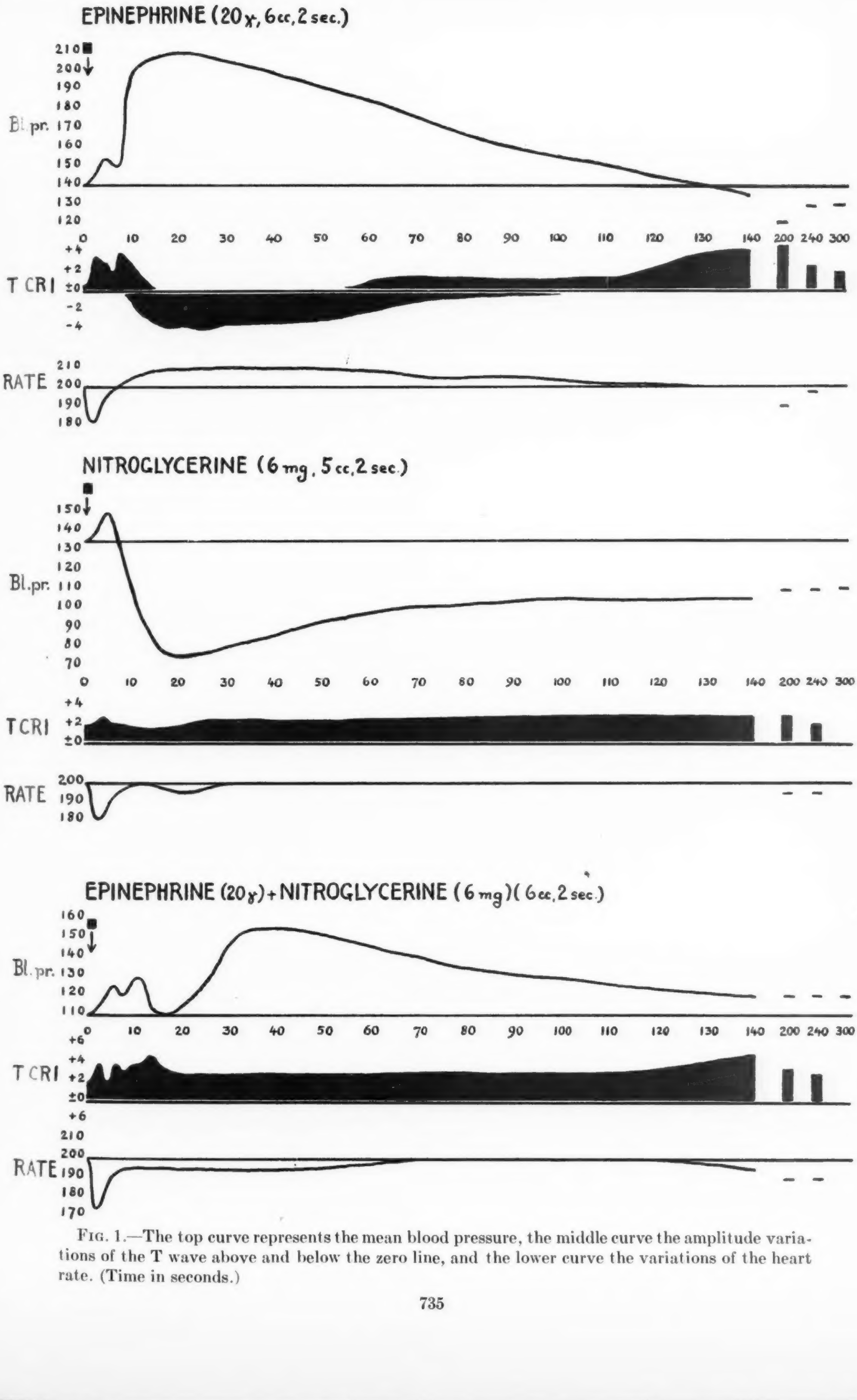

FIG. 1.—The top curve represents the mean blood pressure, the middle curve the amplitude variations of the T wave above and below the zero line, and the lower curve the variations of the heart rate. (Time in seconds.)

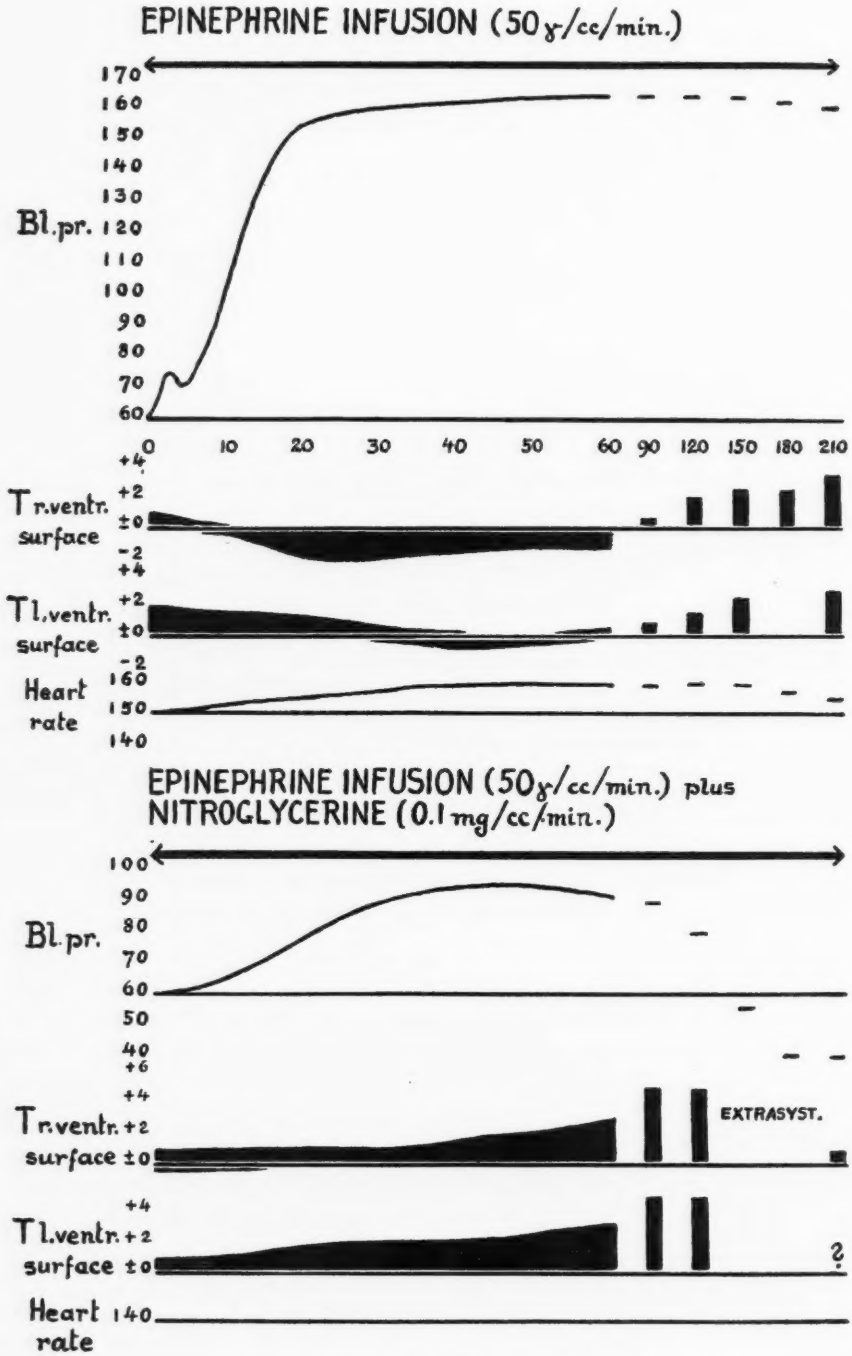

FIG. 2.—See legend, figure 1.

TABLE 1.—*Average Diminution of Adrenergic Effects on the Heart Through Simultaneous or Preceding Intravenous Administration of Nitroglycerin**

Type of Experiments	Cardiac Acceleration	Maximal Depression of T wave (Leads CR_1, CR_4, II)	Number of Experiments
Epinephrine injected or infused	−37%	−33% to −61%	6
Arterenol injected	−29%	−92% to −100%	4
Stimulation of stellate ganglia	−6%†	−61% to −80%	3
Cardiac sympathin injected	−14%	−25% to −100%	3

* Expressed in per cent of the original adrenergic effects (with the action of nitroglycerin alone incorporated into the calculation).

† Nitroglycerin had been injected before stimulation in these experiments. In earlier experiments (Raab and Humphreys[4]) in which nitroglycerin was infused during stimulation, the cardiac acceleration was markedly diminished.

cardiographic effects of sympathin, taking the effects of nitroglycerin as such into account (table 1).

COMMENT

Adrenergic cardiac acceleration and T-wave depression in the atropinized cat, whether produced by injection or infusion of epinephrine or of arterenol or of sympathin, extracted from cattle heart, or by stimulation of the cardiac sympathetic nerve, were diminished or entirely abolished by simultaneous or immediately preceding intravenous injection of nitroglycerin.

A similar effect (normalization of epinephrine-induced electrocardiographic changes through intramuscularly injected nitroglycerin) had been shown in one experiment by Douglas, Gelfand, and Shookhoff[13] in 1937, and Melville[14] has observed a protective action of nitroglycerin against epinephrine-chloroform-induced ventricular premature contractions and fibrillation. Russek and associates[25] were able to abolish the depression of S-T and inversion of T in exercise tests on patients with coronary disease by administering 0.75 mg. of nitroglycerin sublingually. All of these authors interpret the phenomena mentioned as being due

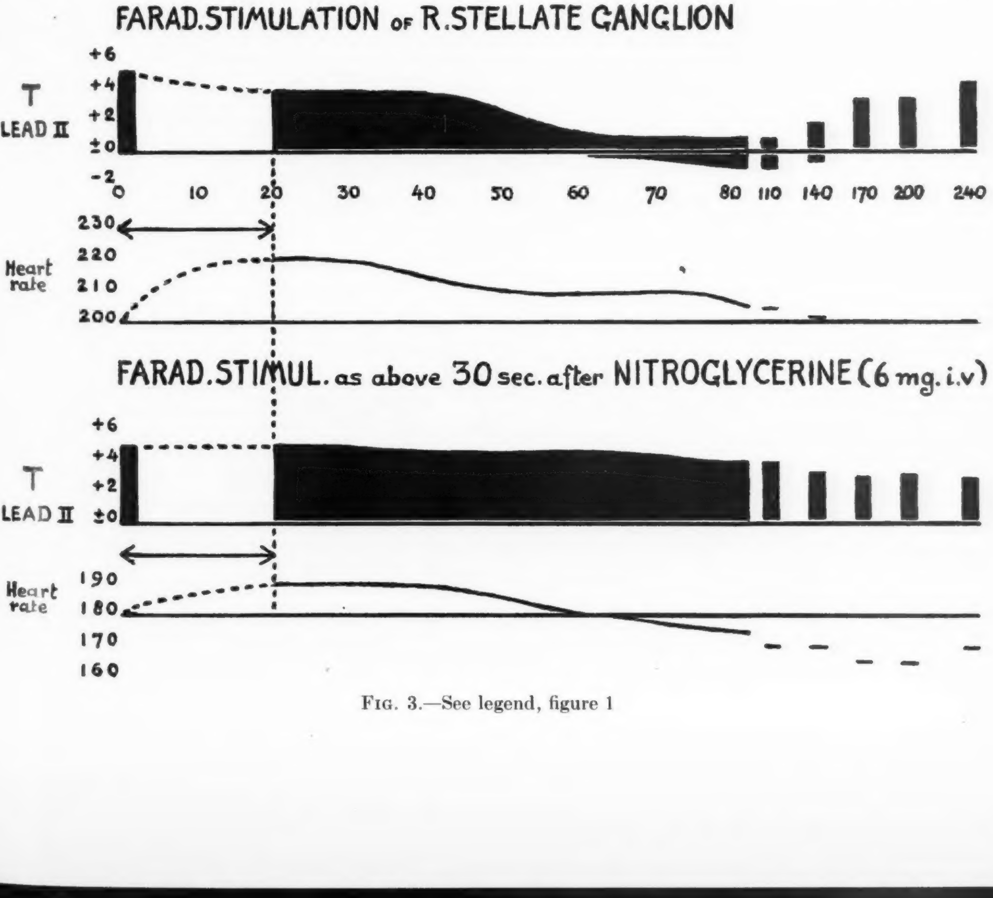

FIG. 3.—See legend, figure 1

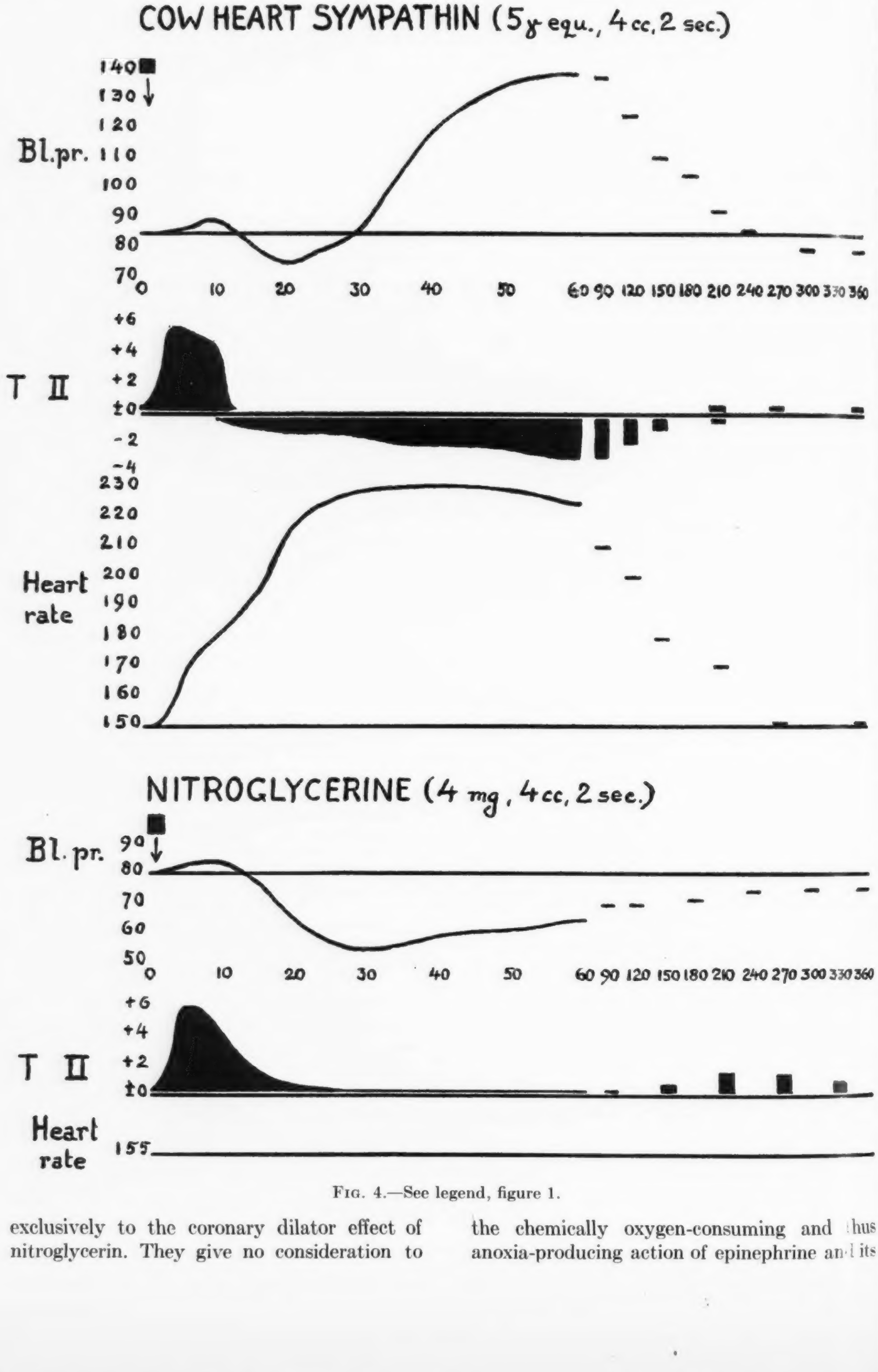

Fig. 4.—See legend, figure 1.

exclusively to the coronary dilator effect of nitroglycerin. They give no consideration to the chemically oxygen-consuming and thus anoxia-producing action of epinephrine and its

derivatives upon the heart, as demonstrated by various investigators,[1, 15, 16, 22, 24, 26] nor to the possibility that nitroglycerin might interfere with this chemical process in the heart muscle cells apart from its relaxing effect upon the coronary vascular muscle cells.[3]

It seems unlikely that the T-wave depressions and inversions, elicited by injected or neurally discharged[17] sympathomimetic amines, should be due to a diminution of the coronary flow, since most investigators agree that the coronary flow is increased rather than decreased by these agents[18, 19, 20] and by stimulation of the cardiac sympathetic fibers.[20, 21, 22, 24, 26] Likewise, it is improbable that the diminution or abolition of the adrenergic T-wave changes by nitroglycerin should be caused by further dilatation of the coronary arteries, nor can the counteraction of nitroglycerin against the sympathomimetic neurohormonal acceleration of the heart be ascribed simply to coronary dilatation.

The diminution of the pressor effects of epinephrine, arterenol, and cardiac sympathin by nitroglycerin is of no significance in accounting for the nitroglycerin-induced diminution of the T wave under depression caused by the sympathomimetic amines, since the T-wave changes have been shown to be entirely independent of the pressor effects of these amines.[23]

Unless we deliberately disregard the functional significance of myocardial metabolism and its alterations through the adreno-sympathogenic neurohormones, we feel compelled to consider the probability that the striking counteraction of nitroglycerin against adrenergic cardiac manifestations is largely, if not entirely, due to a primarily chemical and not merely to a mechanical (coronary dilator) mechanism. Further studies will have to be undertaken before this question can ultimately be settled.

As far as the pathogenesis of angina pectoris is concerned, the therapeutic effect of nitroglycerin cannot be accepted as proof of the existence of a "coronary spasm"; rather does it tend to support the concept of an epineph-

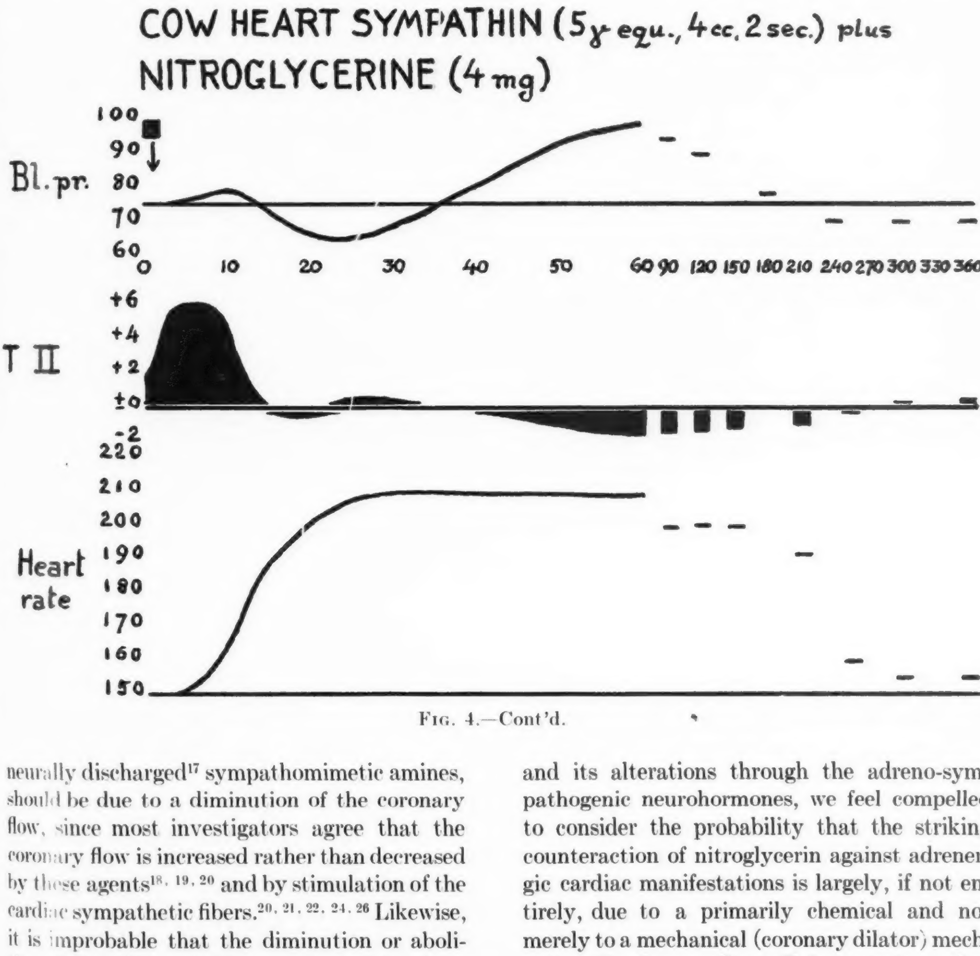

Fig. 4.—Cont'd.

rine-sympathin-induced chemical anoxia of the myocardium as the basis of the anginal syndrome.[2]

Summary

Nitroglycerin strikingly counteracts the typical cardioaccelerator and T-wave depressing effects of epinephrine, arterenol, and neurally discharged or injected cardiac sympathin.

This phenomenon is interpreted as being due to an interference of nitroglycerin with the metabolic, anoxia-producing effects of the sympathomimetic amines on the heart muscle rather than to the familiar coronary dilator action of nitroglycerin, since coronary dilatation is elicited from the beginning by the sympathomimetic amines themselves.

Implications of this concept in relation to the biochemical adrenosympathogenic mechanism of angina pectoris are briefly discussed.

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Heart "Sympathin"

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With the technical assistance of Wilda Gigee, R.N., A.B.

In view of the growing recognition of the pathogenic role of the adrenosympathetic humoral neurotransmitters in the heart muscle as chemical anoxia-producing agents, cardiac "sympathin" was extracted and assayed both colorimetrically and biologically, and some of its chemical and pharmacodynamic properties were studied in detail. It proved to be at least in part identical with nor-epinephrine (arterenol) and to exert effects analogous to those of epinephrine and nor-epinephrine upon blood pressure, heart rate and the electrocardiogram (depression or inversion of the T wave). Its action was intensified by cocaine and counteracted by nitroglycerine.

THE PRESENCE of a cardioacceleratory substance or substances in the heart muscle was discovered independently by Demoor,[1] Haberlandt,[2] and Löwi[3] in the years 1922, 1924 and 1926. While Haberlandt[4] denied, apparently on insufficient evidence, a derivation of his "Herzhormon" from the adreno-sympathetic system, Löwi[5] identified his "Akzeleransstoff" with epinephrine released from the stimulated cardiac sympathetic nerves. Likewise, Cannon and Lissak[6] and Bacq and Fischer[7] considered the sympathomimetic material, isolated by them from the myocardium of cats and man, as being epinephrine. Gaddum and Khayyal[8] and Hoffmann, Hoffmann, Middleton, and Talesnik[9] described the liberation of an "adrenalin-like" substance into the coronary perfusion fluid, especially under the influence of acetylcholine, and McDowall[10] made similar observations with minced heart muscle treated with acetylcholine. The presence in the heart of sympathomimetic catecholamines other than epinephrine has been made probable by colorimetric findings of Shaw[11] and of one of us.[12] Von Euler,[13] having studied active heart extracts very carefully, has come to the conclusion that "the biological effects as well as the chemical tests seem to leave no doubt that the substance responsible for the sympathomimetic actions in the heart extracts is different from adrenalin, and is, instead, intimately related to some substance resembling nor-adrenalin." (Adrenalin and nor-adrenalin are identical with epinephrine and nor-epinephrine respectively.)

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This study was aided, in part, by a grant from the National Heart Institute, and was carried out during the tenure (E.L.) of a Research Fellowship of the American Heart Association.

Attempts at a quantitative assay of sympathomimetic catecholamines in the heart have been undertaken with colorimetric and biologic methods by several investigators (table 1). In order to study the cardiovascular and electrocardiographic effects of the cardiac sympathomimetic amines in detail, as well as to correlate these effects quantitatively with the results of the colorimetric assay of these amines, the following experiments were carried out.

Methods

(a) For the chemical assay of the cardiac catecholamines the colorimetric method of Shaw[11] was used on heart tissue and heart extracts in its modification by one of us.[14]

(b) Extracts of fresh hearts from cows, hogs and humans were prepared with a method, recently described by von Euler[15] for the extraction of sympathomimetic amines from various tissues. It is based on the same principle of isolation of these amines through adsorption by and subsequent elution from aluminum hydroxide as Shaw's colorimetric method and is, therefore, particularly well suited for quantitative comparison of the biological and colorimetric results. Before intravenous injection, the acid extracts were brought to pH 7.0 to 7.5. The dosage of the heart extracts was determined on the basis of their colorimetric readings and expressed in "gamma-equivalents," each gamma-equivalent corresponding to the chromogenic effect of one gamma of epinephrine.

(c) All biologic tests were carried out on atropinized cats under Nembutal anesthesia under artificial respiration and with the adrenals tied off. The extracts and other solutions were injected within 2 seconds into the left femoral vein in volumes of 4 to 6 cc. The blood pressure was recorded from a common carotid artery with a mercury manometer. Coincidence of the electrocardiograms with the blood pressure curve was established through a mechanical connection between the switch of the electrocardiograph and a time marker on the kymograph.

The blood pressure curve, heart rate curve and curves representing the variations of the amplitude of the T wave above and below the electrocardiographic base line, were reconstructed on coordinate paper. Lead II and the chest leads CR_1 and CR_4 or V_1 and V_4 were registered, but only those leads where the T wave was frankly positive at the beginning of the experiment were used for the final analysis.

Table 1.—*Assay of Sympathomimetic Catecholamines in the Heart*

Investigator	Species from which material was obtained	Method used	Calculated gamma per gram of heart muscle
Löwi (5)	Frog	Response of frog heart	1.0–2.0
Shaw (11)	Frog	Colorimetry*	0.3–1.2
Shaw (11)	Rabbit	Colorimetry*	0.015–0.04
Cannon and Lissak (6)	Cat	Cat blood pressure	0.5–0.8
Raab (12, 50)	Rat	Colorimetry*	0.3–1.9
Raab & Humphreys (32)	Cat	Colorimetry*	0.9–1.8
Raab (14)	Man	Colorimetry*	0.3–1.4
Raab (51)	Cow	Colorimetry*, cat bl. pr.	1.2–2.0
Bacq and Fischer (7)	Man	Nictitating membrane	0.3†
von Euler (13)	Cow, horse, cat	Cat blood pressure	5.0

* Based on color units equivalent to 0.001 gamma of epinephrine (see Comment, *Chemical nature*).
† Up to 54% had been lost during the extraction procedure.

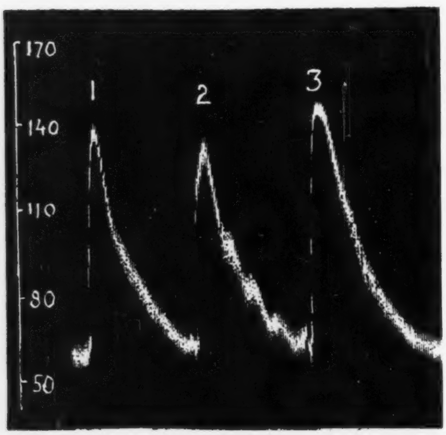

Fig. 1.—Comparative pressor effects of epinephrine, nor-epinephrine (identical with arterenol) and heart sympathin on the blood pressure of the anesthetized, atropinized cat (adrenal glands tied off). (*1*, Epinephrine [5 gamma]; *2*, arterenol [5 gamma]; *3*, cow heart sympathin [5 gamma equ., colorimetrically determined.])

(d) Paper-chromatography was applied to several extracts in an attempt to identify the chemical nature of the active substance, obtained from the heart, by means of the method described by James.[16] The paper strips were developed with potassium ferricyanide. These tests were carried out by Dr. Wm. v. B. Robertson.

(e) The serum potassium concentration was determined with a flame photometer in specimens, withdrawn from the right femoral artery through polyethylene tubing. These assays were also carried out by Dr. Robertson.

Results

Blood pressure. Usually, the pressor effect of freshly prepared heart extracts was equal or near equal to that of amounts of epinephrine which gave qualitatively and quantitatively the same colorimetric readings (fig. 1). Analogous amounts of dl-nor-epinephrine produced pressor effects similar to those elicited by epinephrine (figs. 1 and 2). In several experiments the cardiovascular effects of the heart extracts were compared only with those elicited by dl-nor-epinephrine (identical with dl-arterenol) (figs. 2 and 3, and table 2).

As a rule, the elevation of the blood pressure caused by the heart extracts was preceded by a more or less marked transient fall of blood pressure, ranging from −10 to −45 mm. Hg,

especially when larger doses were used (figs. 2, 3, and 7); the peak of the blood pressure curve was reached somewhat later and the descent of the curve was slower than after injection of epinephrine or nor-epinephrine (figs. 2 and 3). In some experiments, the pressor effect of the heart extract appeared considerably weaker than that of an equi-chromogenic amount of epinephrine or of an analogous amount of nor-epinephrine, especially when large doses were injected (figs. 3 and 6), and in a few instances, the blood pressure elevation was entirely replaced by depression, but in a way which seemed to indicate a fluctuating competition between pressor and depressor influences (fig. 5). The average pressor effect of an average dose of 22 gamma equivalents of cardiac "sympathin" was +43 mm. Hg. (Attempts to identify the interfering depressor material in the heart extracts will be discussed below.)

Heart rate. Regardless of the response of the blood pressure, the heart extracts produced invariably cardiac acceleration. With a dosage of 10–30 (average 22) gamma equivalents, the accelerations ranged from 16 to 65 (average 38) beats per minute. The degree and duration of this cardioacceleratory effect corresponded closely to that produced by equi-chromogenic doses of epinephrine and by analogous doses of nor-epinephrine (table 2). A brief initial period of bradycardia was due to cooling of the sinus node by the injected fluid.

TABLE 2.—*Comparison of the Cardiovascular Effects of Sympathin-Containing Heart Extracts with Those of Epinephrine and dl-Arterenol in Seven Representative Experiments*

Substance injected	Dosage	Maximal rise of:		Maximal depression (mm) of T wave in leads:		
		Blood pressure (mm Hg).	Heart rate (beats per min.)	CR_1	CR_4	II
Heart extract (sympathin)	30 gamma equ.*	+96	+50	−½	−½	—
Epinephrine	30 gamma	+106	+55	−2	−½	—
Heart extract (sympathin)	10 gamma equ.*	+15	+18	—	—	−2½
Epinephrine	10 gamma	+82	+15	—	—	−2½
Heart extract (sympathin)	30 gamma equ.*	+45	+20	—	—	−3½
dl-Arterenol	30 gamma	+125	+15	—	—	−3
Heart extract (sympathin)	30 gamma equ.*	+5	+45	—	—	−1
dl-Arterenol	30 gamma	+85	+25	—	—	−1½
Heart extract (sympathin)	20 gamma equ.*	+50	+65	−2½	—	—
dl-Arterenol	20 gamma	+56	+70	−2½	—	—
Heart extract (sympathin)	15 gamma equ.*	+82	+30	−6	−2½	—
dl-Arterenol	15 gamma	+86	+32	−5	−2¾	—
Heart extract (sympathin)	10 gamma equ.*	±0	+45	—	—	−1¼
dl-Arterenol	10 gamma	+65	+35	—	—	−1

* Colorimetrically determined.

Electrocardiogram. The changes of the electrocardiogram, elicited by the heart extracts, showed a striking analogy with those produced by corresponding amounts of epinephrine or nor-epinephrine[59] (figs. 2 and 3, and table 2). They consisted, as a rule, of a depression and/or inversion of the T wave between the 10th and 40th to 150th seconds, sometimes followed by a transient elevation of the T wave. (A frequently occurring oscillation of the T wave within the first few seconds after injection is unspecific, as it was also seen after injection of plain Ringer solution. It seems to have been due to cooling of the subendocardial ventricular

muscle layers through the injected fluids, which were kept at room temperature.)

In four out of sixteen experiments there was no significant depression of the T wave during the period of the 10th to the 150th second. In these instances, the T wave remained unchanged or became even temporarily elevated. The blood potassium, which was determined in three such experiments, showed an increase which approximately coincided with the elevation of the T waves (fig. 4). Similar reactions had been observed in some experiments with epinephrine and nor-epinephrine, but with increasing doses the typical depression of the T wave could be elicited.

The analogy of the electrocardiographic effects of the heart extracts with those produced by epinephrine and nor-epinephrine was not affected by the presence in the heart extracts of depressor impurities which interfered in varying degrees with their pressor action (fig. 3).

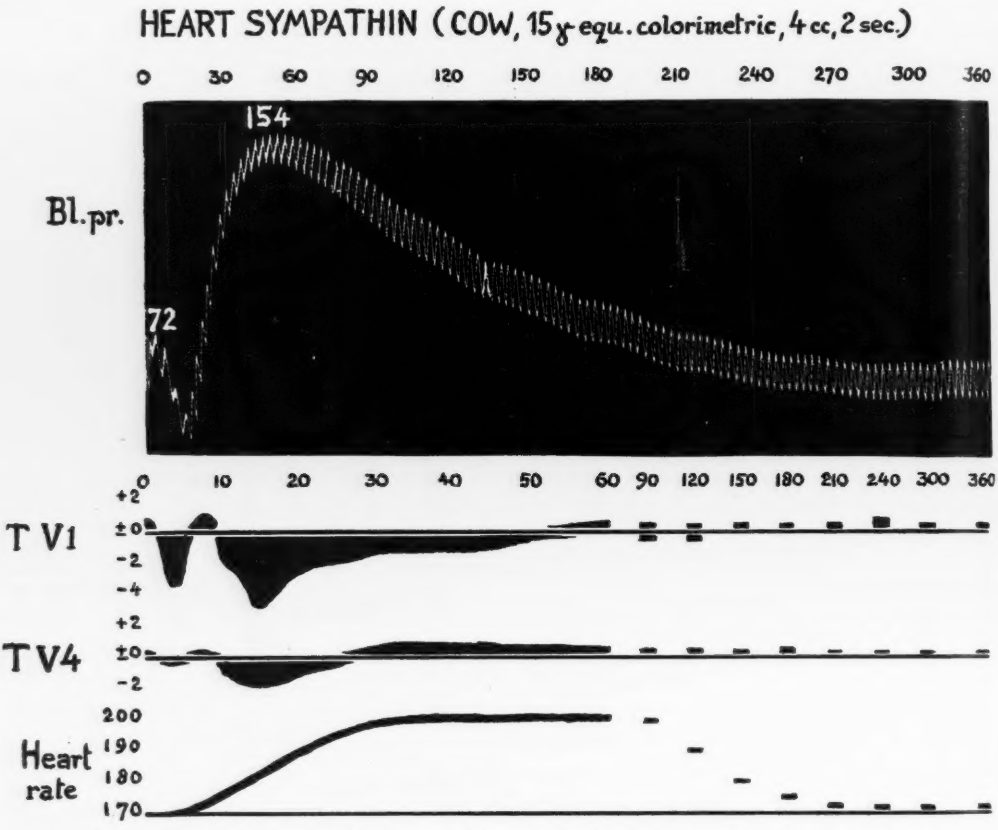

FIG. 2.—The effect of sympathin, extracted from the heart muscle, upon the direction and amplitude of the T waves above and below the electrocardiographic baseline (Leads V_1 and V_4) and upon the heart rate of the atropinized cat is practically identical with that of equi-pressor amounts of nor-epinephrine (identical with arterenol). Time given in seconds from the beginning of the injection. Separate time scales for the kymogram and the plotted curves. (Cont'd on facing page)

Nature of interfering depressor material. The following findings seemed to support the assumption that the usual initial fall of the blood pressure, as well as the occasional marked weakening of the pressor effect of the heart extracts or its replacement by outright depression, might be caused by the presence of histamine or of a histamine-like substance in the heart extract:

(1) Injection of a combination of nor-epinephrine with histamine acid phosphate produced blood pressure curves which were very similar in shape to the curves produced by depressor heart extracts, containing an equivalent amount of colorimetrically determined cardiac sympathin (fig. 5). Two to twenty gamma of histamine base per gamma of nor-epinephrine creased the depressor and enhanced the pressor effect of otherwise depressor heart extracts (fig. 6) but did not eliminate the depressor action. (Neohetramine is incapable of counteracting large doses of histamine[18] [fig. 6]).

(3) Histamine did not interfere with the cardioacceleratory and with the characteristic electrocardiographic effects of nor-epinephrine

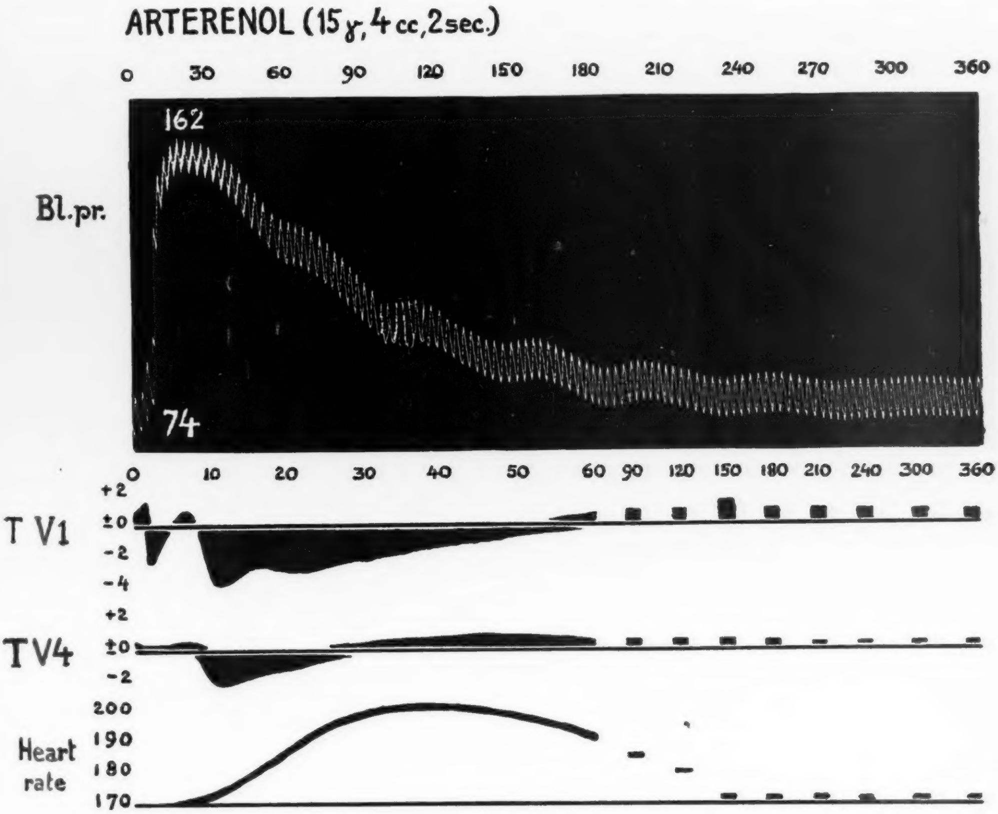

FIG. 2.—*Cont'd.*

were required, in accordance with the individual sensitivity to nor-epinephrine, to imitate the effects of the partly or entirely depressor heart extracts. The histamine content of cattle heart has been estimated as ranging between 10 and 30 gamma per gram of heart muscle,[17] the "sympathin" content between 1.2 and 2.0 gamma per gram.[32]

(2) Pretreatment of the test animals with the antihistaminic agent Neohetramine de-

on the T waves, nor did the depressor material, contained in some heart extracts, interfere with the nor-epinephrine-like electrocardiographic effects of these extracts (figs. 2 and 3).

Despite these observations, which suggested genuine histamine as the interfering depressor material, this assumption must be considered doubtful in view of the fact that histamine acid phosphate, which had been added to the mashed heart muscle before processing, or

which had been subjected alone to the identical procedure, could not be recovered in the final extracts by means of the colorimetric method of Rosenthal and Tabor.[19] Whether another histamine-like substance which cannot be de-

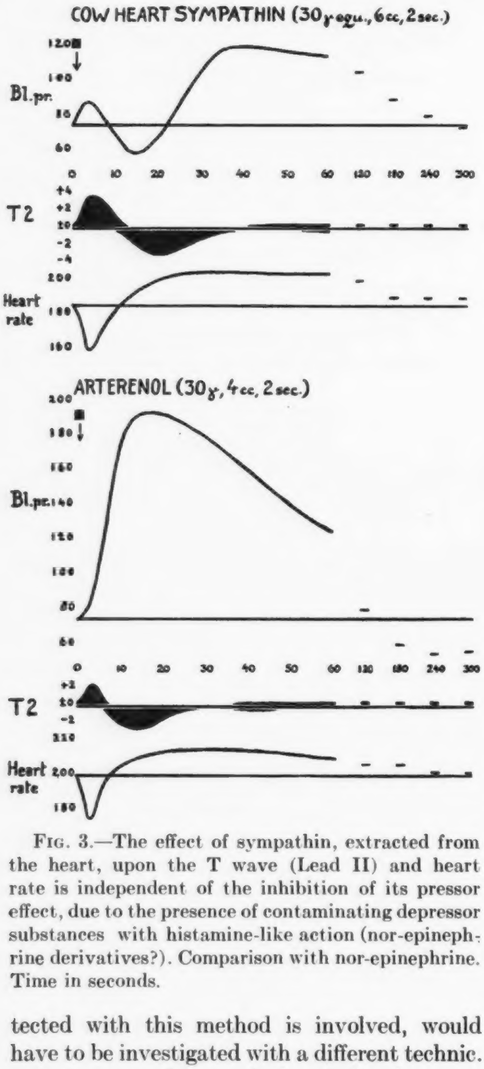

FIG. 3.—The effect of sympathin, extracted from the heart, upon the T wave (Lead II) and heart rate is independent of the inhibition of its pressor effect, due to the presence of contaminating depressor substances with histamine-like action (nor-epinephrine derivatives?). Comparison with nor-epinephrine. Time in seconds.

tected with this method is involved, would have to be investigated with a different technic.

Attempts to destroy the interfering depressor material by incubating either the heart muscle or the final extracts with histaminase-containing tissue extracts at pH 7.5 gave inconclusive results, as the added extracts produced strong depressor effects by themselves.

The fact that von Euler's heart extracts (after having been purified from other contaminants) appeared to be relatively free from depressor actions, has been attributed by him[20] to the difference in dosage, in that his experiments were carried out with much smaller doses than those which we needed in order to provoke electrocardiographic responses.

In view of the existence of N-alkyl-homologues of epinephrine with similar cardioaccel-eratory and T-wave depressing,[21–23] as well as chromogenic, properties, but with a vasodepressor action,[21, 23–25] the possible presence of such substances in the heart extracts was also taken into consideration. However, this appears most unlikely, as the combined injection of such substances (N-isopropyl- and N-ethyl-epinephrine) with nor-epinephrine produced blood pressure curves which differed significantly from those produced by partly depressor heart extracts, in that the depressor effect occurred always belatedly after an initial elevation.

Finally, the possibility of the presence of unidentified depressor derivatives from nor-epinephrine must be considered.[57]

Modification of cardiovascular effects of heart sympathin by cocaine. In four experiments, heart extracts (5–30 gamma equivalents) were injected before and after cocaine (30–50 mg. intraperitoneally). An intensification of the pressor effect (fig. 7) like that which is characteristic for both epinephrine and nor-epinephrine,[13] and a rather insignificant increase of cardiac acceleration were observed, as far as interfering arrhythmias (atrioventricular block, ventricular fibrillation and cardiac alternans which occurred only after cocaine pretreatment) permitted. In two experiments, the T-wave depressing effect of the heart extracts was markedly intensified after cocaine; in two other experiments, with an elevation of the T wave, this was slightly to markedly diminished in two leads.

Modification of cardiovascular effects of heart sympathin by nitroglycerine. In view of the fact that nitroglycerine had been found to weaken not only the pressor but also the cardioacceleratory and T-wave depressing effects of epinephrine and nor-epinephrine,[26] three experiments

were carried out in which heart extracts were injected alone and simultaneously with nitroglycerine (4–6 mg. intravenously), as well in that the T-wave depressing effect of heart sympathin (5–30 gamma equivalents) was weakened or entirely abolished.

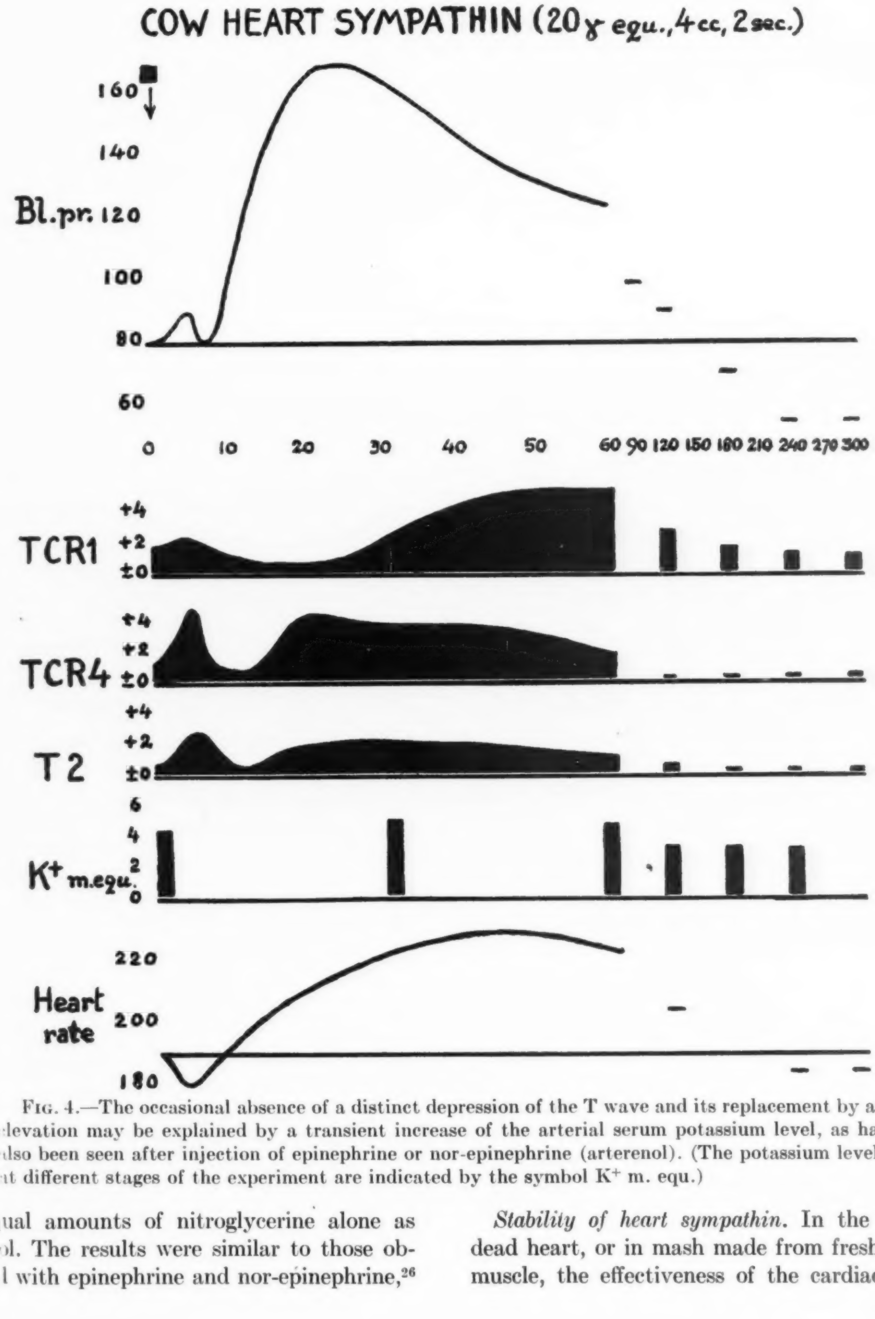

FIG. 4.—The occasional absence of a distinct depression of the T wave and its replacement by an elevation may be explained by a transient increase of the arterial serum potassium level, as has also been seen after injection of epinephrine or nor-epinephrine (arterenol). (The potassium levels at different stages of the experiment are indicated by the symbol K^+ m. equ.)

as equal amounts of nitroglycerine alone as control. The results were similar to those obtained with epinephrine and nor-epinephrine,[26]

Stability of heart sympathin. In the intact dead heart, or in mash made from fresh heart muscle, the effectiveness of the cardiac sym-

pathin began to decline after about twenty-four hours in the refrigerator, and it almost disappeared within forty-eight hours, while the acid extracts remained fully active for several days.

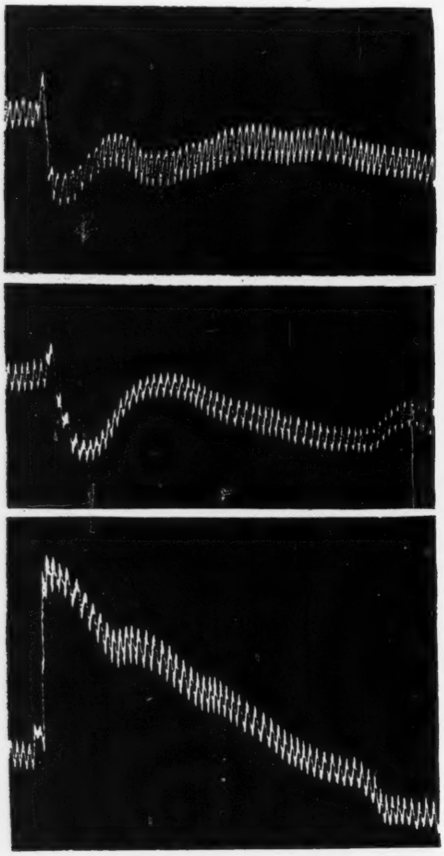

FIG. 5.—In some heart extracts, the pressor action of sympathin (determined colorimetrically) seems to be entirely overshadowed by depressor contaminants. The depressor curve, elicited by these extracts, can be imitated by the combination of analogous amounts of nor-epinephrine (arterenol) with histamine. (Top curve, cow heart sympathin [10 gamma equ.]; middle curve, dl-arterenol [10 gamma] + histamine acid phosphate [600 gamma]; bottom curve, dl-arterenol [10 gamma].)

Paper chromatography of heart extracts. This procedure gave definite evidence of the presence of nor-epinephrine in the heart extracts. The R_f value and the color, obtained upon development, were identical with those of nor-epinephrine. Since no quantitative evaluation of the nor-epinephrine, detected by paper chromatography, has yet been undertaken, the question remains open as to whether the chromogenic and biologically active material in the heart muscle consists entirely of nor-epineph-

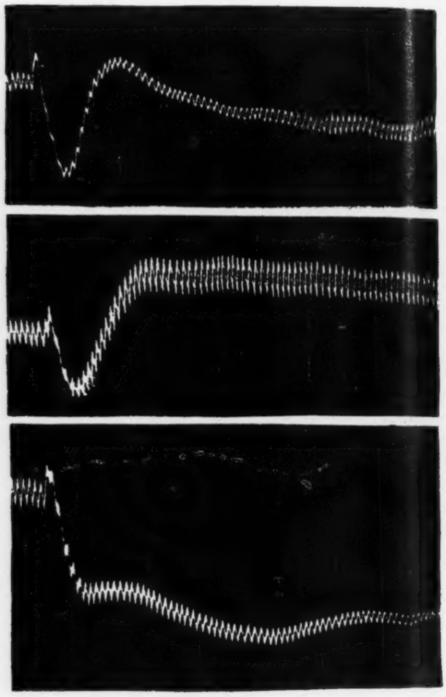

FIG. 6.—The pressor properties of sympathin, contained in some prevailingly depressor heart extracts (colorimetrically determined) can be partly brought to light by pretreatment of the test animal with an antihistaminic agent (Neohetramine) which, however, is incapable of counteracting large doses of histamine. (Top curve, cow heart sympathin [30 gamma equ.]; Middle, cow heart sympathin [30 gamma equ.] after Neohetramine [12 mg./kg.]; bottom curve, histamine acid phosphate [1800 gamma] after Neohetramine [12 mg./Kg.].)

rine or whether some other undefined related substances are also present. However, no other catecholamines, including epinephrine, which are capable of forming adrenochromes, could be demonstrated in the heart extracts.

COMMENT

Our results confirm the statements of other investigators regarding the presence in the

heart of sympathomimetic amines (heart "sympathin"), possessing chromogenic and biologic properties similar to those of epinephrine and particularly of nor-epinephrine. The cardiovascular effects of heart sympathin, as well as its chemical nature and pathophysiologic significance, have been studied in further detail.

Cardiovascular effects. In addition to the pressor and cardioacceleratory effects, the action

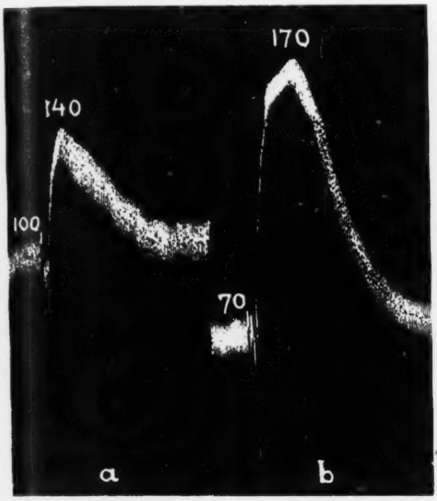

FIG. 7.—The pressor action of heart sympathin (like that of epinephrine and of nor-epinephrine) is markedly enhanced by pretreatment of the test animal with cocaine. (*a*, Cow heart sympathin [10 gamma equ.]; *b*, the same after 40 mg. cocaine.)

of cardiac sympathin upon the electrocardiogram was found to be practically identical with that exerted by equi-chromogenic and equipressor amounts of epinephrine and by analogous amounts of nor-epinephrine, even in those instances in which the pressor effect was partially or entirely masked by contamination of the heart extracts with depressor impurities.

The characteristic depression and/or inversion of the T wave, elicited by extracted and injected cardiac sympathin, like those elicited by injected epinephrine and nor-epinephrine, or by stimulation of the cardiac sympathetic nerves[26] (sympathin discharge), are attributable to the specific action of these sympathomimetic amines and their derivatives[40] upon the myocardial cell metabolism. This chemical action results in excessive, wasteful oxygen consumption by the heart muscle and in consecutive myocardial hypoxia, despite simultaneous coronary dilatation which does not suffice to compensate fully for the rapid consumption of oxygen.[38, 39, 41, 53] Recent observations have shown a remarkable degree of independence of the electrocardiogram from the coronary blood flow.[52]

According to Kisch,[40] the stimulation of oxygen consumption is not due solely to epinephrine itself, but rather to a quinoid oxidation product of epinephrine (omega adrenochrome) which is formed through enzymatic interference in the tissues. This view seems to be compatible with our recent observation[58] that doses of adrenochrome which exert only a slight pressor activity can elicit a T-wave inverting (hypoxia-producing) effect on the electrocardiogram.

In a few instances, the sympathin-containing heart extracts failed to depress the T wave. This was probably due to a simultaneous increase of serum potassium which is known to elevate the T wave.[27] Epinephrine mobilizes potassium from the liver[23] and the same seems to be true regarding cardiac sympathin (fig. 4).

Like the cardiovascular effects of epinephrine and nor-epinephrine, those of cardiac sympathin were partly accentuated by cocaine (fig. 7) and weakened or abolished by nitroglycerine (blood pressure, T-wave depression).

Chemical nature. As far as the chemical identity of the chromogenic and biologically active heart sympathin is concerned, it can be stated on the basis of paper-chromatographic tests, that nor-epinephrine constitutes at least a substantial part of it and may possibly be identical with it in its entirety. This would be compatible with the pharmacodynamic and colorimetric tests, carried out by von Euler.[13] However, if we do assume a total identity of the chromogenic and sympathomimetic material, extracted from the heart, with nor-epinephrine, there remains a discrepancy to be explained, in that the maximally pressor extracts appeared both equi-chromogenic and equi-pressor with epinephrine, while the color effect of pure nor-epinephrine is weaker (about one third)[29, 51] and its pressor effect stronger (about twice)[30, 31] compared with those of epinephrine. It is pos-

sible that even the maximal pressor effects, produced by heart extracts, were the results of a compromise between a per se stronger nor-epinephrine action and the counteraction of interfering vasodepressor contaminants which, in some instances, were, in fact, powerful enough to dominate the picture.

Epinephrine was not demonstrable by paper-chromatography in the hearts of animals which had been killed rapidly in the slaughterhouse. In case of an identity of all cardiac sympathin with nor-epinephrine, the colorimetric readings, obtained with the method of Shaw[11, 12, 14, 32, 50, 51] would have to be multiplied by three, and, thus, would closely approach the figure given by von Euler[13] (see table 1).

Origin. The original formation of cardiac sympathin or of its immediate precursors takes place, in all likelihood, within the ganglia and postganglionic fibers of the cardiac sympathetic nerves, from which it is discharged through a process of "neurosecretion" into the myocardial effector cells. Stimulation of the cardiac sympathetic nerves has been shown to be followed by an increase of the myocardial sympathin concentration,[32] cardiac denervation, on the contrary, by a partial depletion.[33] The fact that this depletion is never a complete one, seems to support the contention that neurosecretory sympathetic structures exist also inside the heart muscle itself, as suggested by both morphologic[34–36] and biologic[9, 37, 49] findings. Finally, the heart muscle possesses an outstanding ability to absorb and accumulate epinephrine and related compounds from the circulating blood.[14] Nor-epinephrine has only recently been recognized as forming a substantial part of the adrenal medullary secretion.[54–56]

An increase of the concentration of epinephrine-like substances in the heart has been observed colorimetrically not only after injection of epinephrine, but also after physical exercise, exposure to cold, and administration of agents which are known to elicit the discharge of epinephrine and nor-epinephrine (acetylcholine,[47] insulin[14]) finally also in thiamin deficiency.[48]

Pathogenic significance. The presence in the heart of relatively large quantities of such a powerful and potentially injurious hypoxia-producing agent as nor-epinephrine, must be considered as being of fundamental significance for the understanding of many physiologic and pathologic functional states of the heart.[46]

Abnormally high concentrations of catecholamines, either identical with or related to nor-epinephrine and epinephrine, have been demonstrated colorimetrically in the hearts of individuals who had died in uremia,[42] in congestive cardiac failure[14] or who had succumbed to a sudden, otherwise unexplained cardiac death.[43–45]

The probable role of sympathomimetic amines in the heart muscle in the pathogenic mechanism of thyrotoxic heart disease and of angina pectoris has been discussed elsewhere.[46]

Summary

The heart muscle of cattle, hogs and humans was shown to contain relatively large amounts of pharmacodynamically potent sympathomimetic material ("sympathin") which was found to be at least in part chemically identical with nor-epinephrine (arterenol), and which may be possibly identical with nor-epinephrine in its entirety.

When extracted from heart muscle and injected into atropinized cats in colorimetrically determined doses, heart sympathin elicited cardiovascular effects (elevation of blood pressure, cardiac acceleration, depression and/or inversion of the T wave) equivalent to those of equi-pressor and equi-chromogenic doses of epinephrine or analogous doses of nor-epinephrine. In some extracts, the vasopressor effect was largely masked by histamine-like-acting depressor contaminants which, however, were not identical with histamine (nor-epinephrine derivatives?), and which did not interfere with the specific cardiac effects of heart sympathin.

The action of heart sympathin was modified by cocaine and by nitroglycerine in the same manner as that of epinephrine and nor-epinephrine.

The neurosecretory origin and the pathophysiological significance of heart sympathin were briefly discussed, with particular emphasis on the widely disregarded ability of epinephrine and nor-epinephrine to elicit hypoxia of the heart muscle by chemically inducing an excessive and wasteful oxygen consumption in

the myocardium, irrespective of coronary blood flow.

ACKNOWLEDGMENTS

We are indebted to Dr. William v. B. Robertson for carrying out the paper-chromatographic tests and serum potassium determinations, and to Dr. M. L. Tainter of the Sterling-Winthrop Research Institute for the supply of dl-arterenol (dl-norepinephrine).

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Bernheim's Syndrome: Report of a Case

By Donald H. Atlas, M.D., Ph.D., Herman L. Eisenberg, M.D., and Peter Gaberman, M.D.

In the controversial Bernheim's syndrome, right ventricular failure can be produced by hypertrophy and dilatation of the left ventricle with encroachment of the intraventricular septum into the cavity of the right ventricle, forming a barrier to the flow of blood into the right ventricle. A case is reported in which this syndrome was diagnosed during life and confirmed at autopsy. Hearts of similar weight with left ventricular hypertrophy were sectioned in the same plane for comparative purposes.

In 1908, Bernheim[1] first described a symptom complex that has since been the subject of considerable controversy. In this and subsequent publications, Bernheim[2] presented case reports to illustrate his belief that right ventricular failure can occasionally supervene from eccentric left ventricular hypertrophy with minimal hypertrophy and dilatation of the right ventricle. He observed that this hypertrophy and dilatation of the left ventricle can in certain cases produce encroachment of the interventricular septum upon the cavity of the right ventricle in its apical half to form a stenosis or physical barrier to the flow of blood, with resultant systemic venous engorgement.

It was Bernheim's contention that the symptom complex resulting from this stenosis could be diagnosed during life if the patient's symptoms were carefully evaluated. He claimed that in his cases the symptoms and signs of right ventricular failure preceded and predominated over those of left ventricular failure until the terminal stages, when both were markedly evident. This evidence of pulmonary congestion when cardiac failure is advanced does not preclude the existence of this entity as claimed by some.[3]

There are numerous references to this syndrome in continental literature, but in the English language journals, reports are conspicuously scarce. Master and Russell[4] reported a complex case of acute coronary artery occlusion with interventricular septal perforation and occlusion of the superior vena cava. Because of the multiplicity of cardiac involvement, it is doubtful that this case can be classified as an example of Bernheim's syndrome. Glushein and Geer[5] reported a case in which the diagnosis was corroborated by postmortem examination.

The most complete review of the subject in the English language is the report of Russek and Zohman.[6] They stated that while the majority of cardiac patients with hypertrophy of the left ventricle manifest visceral congestion and edema only after dyspnea and pulmonary congestion have been present for some time, the former symptoms are the first to appear when stenosis of the right ventricle has supervened. They presented 3 cases of Bernheim's syndrome, 2 of which were diagnosed ante mortem and confirmed at autopsy, and one of which was established only post mortem.

The existence of this syndrome has been questioned by many cardiologists; and most standard textbooks dealing with cardiovascular diseases either fail to consider it or actually deny its existence. No reference to the condition could be found in the works of Levine[7] and of Stroud,[8] and White[9] does not accept the existence of the syndrome. Although no specific mention is made of the syndrome of Bernheim, references to this displacement of the septum into the right ventricle are to be found in the texts of both Schwedel[10] and Harrison.[11]

Fishberg[12] appears to be convinced that the condition is an entity and can occasionally be observed. He states that he has observed in "many necropsies on patients with hypertension or aortic insufficiency and severe systemic venous stasis . . . that the septum of the enormously hypertrophied and dilated left ven-

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tricle bulged so far to the right that a large part of the cavity of the right ventricle was obliterated."

He concludes that two mechanisms may result in systemic venous engorgement in essential hypertension: (1) the commonly accepted mechanism of left ventricular failure and increased pulmonary tension, and secondary right ventricular hypertrophy and dilatation; and (2) bulging of the septum into the right ventricle with obstruction to the flow of blood from the right auricle.

TABLE 1.—*Comparison of Control Series of Four Hypertensive Hearts with the Heart from a Patient with Bernheim's Syndrome*

	Heart Weight	Maximum Thickness of	
		Wall of Right Ventricle	Wall of Left Ventricle
	grams	*mm.*	*mm.*
Bernheim's syndrome	700	7	22
Hypertensive heart	625	7	24
Hypertensive heart	950	12	30
Hypertensive heart	680	7	23
Hypertensive heart	715	9	17

Note: The weights and measurements of the ventricular walls of the control series of hypertensive hearts, selected at random, compared with the weight and measurements of the heart of our patient with the Bernheim syndrome, show that the weight of the heart, the thickness of the walls, and degree of hypertrophy bear no relationship to the amount of encroachment by the septum. (The actual measurement of the capacity of the right ventricular cavity or the distance from the septum to the wall of the right ventricle would be of great value, but was not practicable on autopsied hearts.)

Further evidence that a physical barrier can produce this symptom complex can be found in the rare case reports of tumors within the right side of the heart. In the case reported by Amsterdam and his collaborators[13] the chronologic chain of events is strikingly similar to that in our case.

It is our purpose to present a case report in which this syndrome was diagnosed ante mortem in a patient with hypertensive arteriosclerotic heart disease and confirmed at autopsy by sectioning the heart in a transverse plane. As a basis for comparison, four hearts* of approximately the same size and weight were sectioned in the same plane (table 1 and fig. 2).

While it is self-evident that the transverse measurement of the ventricular cavities depends to some extent upon the level of transsection (viz., the closer to the apex, the smaller the width of both cavities), the proportionate size of the two cavities should be the same in all transverse sections.

CASE REPORT

The patient, a 54 year old white woman of Italian descent, was first admitted to Mount Sinai Hospital on April 9, 1948, with a history of having had high blood pressure and an enlarged liver for the preceding three years. One year prior to admission she noticed a progressive swelling of the ankles and a blueness of the lips. Several months later she noticed slight shortness of breath on exertion. She complained of no orthopnea or paroxysmal nocturnal dyspnea and was ambulatory despite the pedal edema. Physical examination revealed an apprehensive white woman, whose cyanosis was markedly out of proportion to her dyspnea. Although mildly dyspneic, she was able to lie flat in bed comfortably. This position, however, markedly intensified her cyanosis. Her blood pressure was 240/100, temperature 98.6 F., respiration rate 24, and pulse rate 82 and regular. Funduscopic examination revealed a moderate degree of hypertensive retinopathy. There was marked jugular vein engorgement bilaterally. Fine, moist râles were audible over the left lower lobe posteriorly. The heart borders were markedly enlarged, both to the right and left. The heart tones were clear, the rhythm regular, and a systolic murmur, soft and blowing, was audible at the apex. The aortic second sound was accentuated. The abdomen was obese and soft. The liver edge was palpable 10 cm. below the right costal margin; it was smooth, firm, nontender, and nonpulsating. The spleen was easily palpable 3 cm. below the left costal region; it was smooth and firm. The lower extremities revealed a moderate pitting edema, bilaterally equal, extending to the knees. There was slight sacral edema. Venous pressure was 19 mm. of water.

On the cardiac regimen of mercurial diuretics, digitalis, and a low-salt diet, the edema subsided, although the cyanosis and enlargement of the liver and spleen remained unchanged. The patient was discharged on April 15, 1948, and readmitted on June 2, 1948, in a state of congestive failure.

* Specimens obtained from the Department of Pathology, Cook County Hospital, through the courtesy of Hektoen Institute for Medical Research, Chicago, Ill.

Since a diagnosis of Bernheim's syndrome was considered, angiocardiography was attempted but was unsuccessful because of technical difficulties and the poor condition of the patient. The patient expired eighteen hours after the second admission.

*X ray Report.** The posteroanterior roentgenogram of the chest made on April 10, 1948, disclosed the normal subdivisions flattened and obscured by bronchopneumonic infiltration, and congestion of the hilar areas (fig. 3). The vascular pedicle was widened and the aortic knob prominent. The transverse diameter of the heart was considerably enlarged, the measurements being M.R. = 9.1 cm., M.L. = 10.5 centimeters. The film exposed in the left oblique diameter demonstrated marked enlargement of the left ventricle, especially along its in-flow tract. Absence of left auricular enlargement to the right, left, or posteriorly in the posteroanterior view is important. The barium-filled esophagus remained straight in the left oblique view and the angle of the bifurcation of the trachea was not visibly widened.

* Interpretation by Dr. Julian Arendt, Chief of the Roentgenology Department, Mount Sinai Hospital.

The enlargement of the contour of the right side of the heart into the right lung field and the displacement of the esophagus backward as was seen in the right oblique view were probably due to right auricular enlargement. Thus the roentgen-ray demonstration of left ventricular enlargement and right auricular dilatation without marked enlargement of the left auricle and right ventricle was compatible with the clinical diagnosis of Bernheim's syndrome. However, in the absence of well-defined demarcation points, inner structural changes and chamber boundaries could not be identified with assurance.

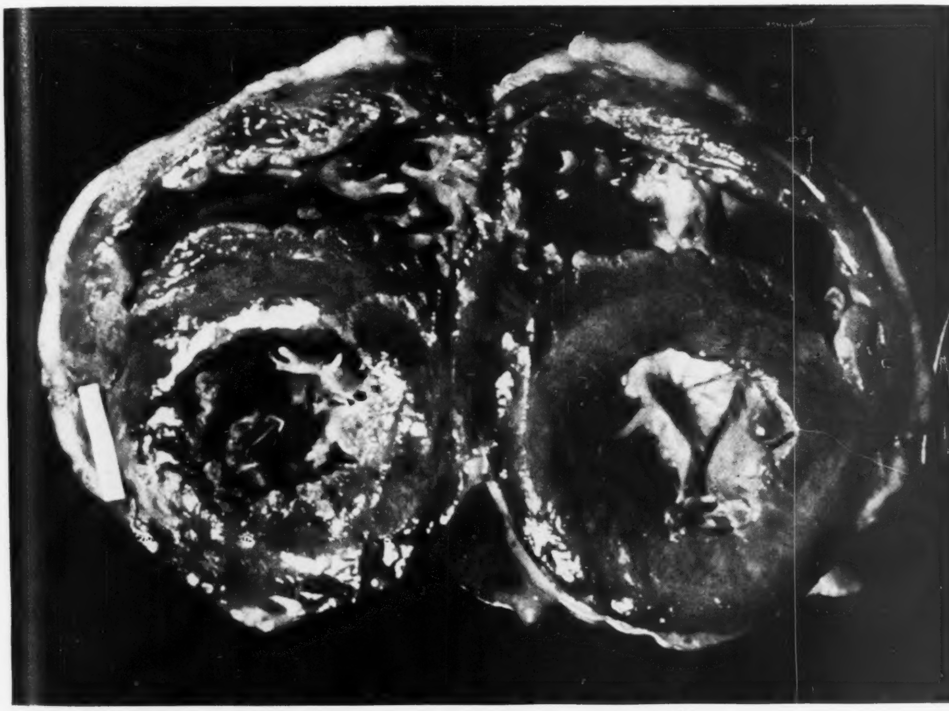

FIG. 1.—Photograph of the heart of our patient showing bulging of the interventricular septum, most marked in apical portion of heart (left side of photograph).

Essential Laboratory Data. Laboratory findings on the first admission were as follows: the red blood cell count was 4,600,000 and the white blood cell count 8,300 per cu. mm. of blood; the differential count gave normal values. The fasting blood sugar was 115 mg. per 100 cc. of blood and the urea nitrogen value 24.9 mg. per 100 cubic centimeters. The total protein measured 6.5 grams per 100 cc. of serum, albumin 4.5, and globulin 2 grams per 100 cc. of serum. Urinalysis was negative for sugar and casts, and showed a 1+ albumin reaction. Five to 6 red blood cells and 20 to 25 white blood cells per

high-powered field were found. The electrocardiographic pattern was that of a left ventricular strain.

*Autopsy Report.** No fluid was found in the pleural and abdominal cavities but the pericardial sac contained about 20 to 30 cc. of clear fluid.

The right lung weighed 510 grams and the left 450 grams. The small bronchi and bronchioli of both lungs were filled with mucus and thick, purulent exudate. In the upper and lower lobes, especially in the central areas, there were numerous bronchopneumonic foci. The mediastinal and basal portion of the left lower lobe was atelectatic owing to pressure of the enlarged and bulging left ventricle.

The left auricular appendage measured 4 by 1.5 cm. and its wall was 1.5 mm. thick. A transverse section through both ventricles was made 5.5 cm. below the base (fig. 1). The sectioned surface showed a round, target-shaped left ventricular cavity and a narrow, sickle-shaped right ventricular cavity. The thickness of the wall of the left ventricle was everywhere alike, measuring 22 millimeters. The maximal thickness of the septum also measured 22 millimeters. The wall of the right ventricle was 7 mm. thick. All of the valves were competent. The coronary arteries were wide and grossly patent and the intima showed occasional yellow plaques of arterio-

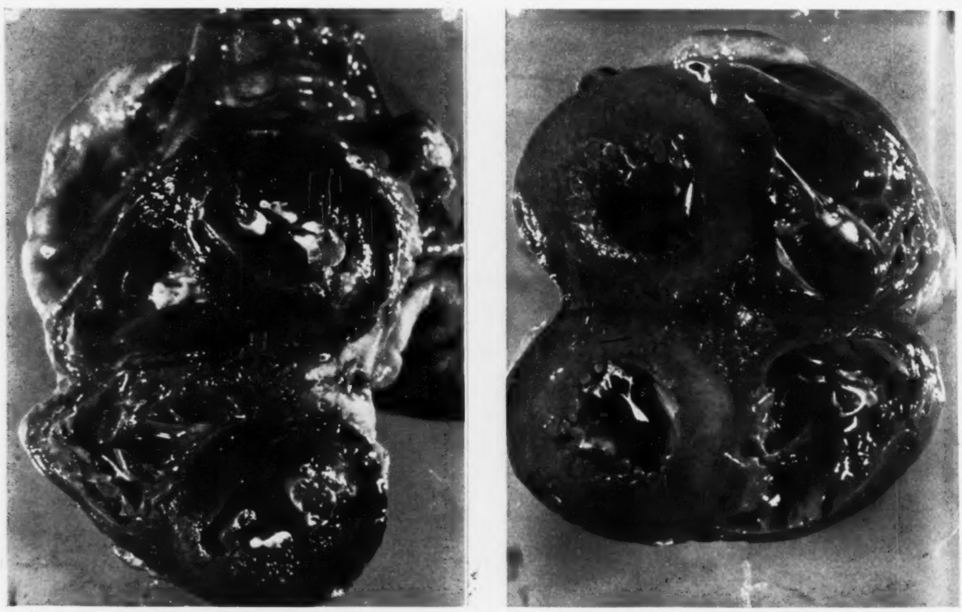

FIG. 2.—Photographs of two markedly hypertrophied hearts of hypertensive patients whose symptoms followed the usual course. The apical section is the inferior half.

sclerosis. The left auricle was considerably smaller than the right auricle and its wall was 2 mm. thick, while that of the right auricle was 4 mm. thick. No gross scars were seen on the cut surface of the myocardium. Numerous atheromatous plaques were visible on the descending aorta and a few could be seen on the ascending aorta.

The liver margin extended 12 cm. below the xiphoid process. The surface was smooth and glistening. The sectioned surface was smooth and revealed chronic congestion with large red acenar centers and light-yellow peripheries. The kidneys weighed 300 grams together, were of usual size, and their sectioned surface showed the general structure well preserved. The spleen was enlarged, weighing 400 grams.

The heart was enlarged, weighing 700 grams. The apex was rounded, and was formed predominantly by the left ventricle. The right auricular appendage measured 8 by 5.5 cm. and its wall was 4 mm. thick.

No abnormalities were seen in the adrenal glands, gall bladder, gastrointestinal tract, and pancreas.

On microscopic examination, sections of the heart revealed hypertrophy of the muscle fibers, and in many places small scars replaced muscle fibers, many of which were disintegrating. Numerous newly formed capillaries were seen in all of these small scars.

* The postmortem examination was done by pathologists Dr. Ernst Loeffler and Dr. Israel Davidsohn.

FIG. 3.—Posteroanterior roentgenogram of chest showing marked hypertrophy and dilatation

Sections of the lung revealed mucopurulent exudate from many of the large bronchi and bronchioli. The loose connective tissue around the bronchi was frequently infiltrated with leukocytes, eosinophiles, and round cells. The alveolar walls were thick and congested and were filled in many places with accumulations of heart failure cells. In other areas the alveoli were found to be filled with edema fluid. Also present were a few foci of bronchopneumonia.

Sections of the liver revealed the structure generally well preserved. The central veins and the sinusoids were somewhat dilated. Sections of the kidney revealed only moderate congestion as did sections of the spleen.

The anatomic diagnosis was: (1) Hypertensive heart disease with eccentric hypertrophy of both ventricles, predominantly of the left; hypertrophy and dilatation of the right auricle; compression of the right ventricle by bulging of the septum (Bernheim's syndrome). (2) Acute mucopurulent bronchitis and bronchiolitis. (3) Bronchopneumonia. (4) Compression atelectasis of the left lower lobe. (5) Chronic passive congestion of the spleen, liver, and gastrointestinal tract.

DISCUSSION

This patient presented the history, symptoms, and objective findings that fulfilled the tenets of the syndrome of Bernheim. She was known to have had severe hypertension of several years' duration. Her earliest and predominant symptoms were those of right ventricular failure. There was no evidence of conditions associated with cor pulmonale. The diagnosis was established clinically and autopsy confirmed the diagnosis.

The most striking anatomic feature of this case, aside from the septal change, was the marked hypertrophy and dilatation of the right auricle and right auricular appendage. The right appendage measured 8 by 5.5 cm. and its wall was 4 mm. in thickness, whereas the left appendage measured 4 by 1.5 cm. and its wall was 1.5 mm. thick. The right auricle was also found to be markedly hypertrophied and dilated; the left auricle was normal.

The presence of pulmonary congestion and some hypertrophy of the right ventricle in our case, and pulmonary infarction in the other case reports, in our opinion, does not exclude the diagnosis of this syndrome as is contended by Evans and White.[3] We believe, as does Fishberg,[12] that both pulmonary congestion, with resultant pulmonary hypertension, and compression of the right ventricular cavity by the septum can exist simultaneously. The factor which is dominant will determine the chronological sequence of events. Moreover, pulmonary congestion and infarction are often found terminally in association with advanced heart failure, regardless of the underlying initial etiologic basis and mechanism.

The existence of the syndrome is, of course, predicated on the backward failure theory of congestive failure and does not take under consideration the recent studies on sodium balance, venous tone, and blood volume. It is our feeling that the physical mechanism described here may be only an additional factor, and is not incompatible with the more recent theories of congestive failure and edema formation.

The question remains to be answered why the symptom complex as described by Bernheim and others is observed so infrequently, when the conditions which may produce it are so common. Interference with the blood supply of the septum, either congenital or as a result of acquired vascular occlusion, may be a factor. Marked variations in the contour and convexity of the septum may be seen in the transverse sections of post-mortem injected human hearts in which septal infarction is present.[14]

Summary

A case report is presented in which a diagnosis of the syndrome of Bernheim was made during life and confirmed at autopsy by a section of the heart in a transverse plane.

As a basis for comparison, four hearts of equivalent weights with markedly hypertrophied left ventricles were sectioned in the same plane.

This problem deserves further investigation by the more recently refined technic of cardiac catheterization and angiocardiography.

Acknowledgment

The authors wish to express their appreciation to Dr. David Lembert for the privilege of studying this case.

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The Syndrome of Bernheim as a Clinical Entity

By Henry I. Russek, M.D., and Burton L. Zohman, M.D.

Can the right ventricle become partially obliterated by a bulging and hypertrophied interventricular septum so as to produce the clinical picture of isolated right heart failure? If so, the syndrome of Bernheim must be accepted as a distinct clinico-pathologic entity. The authors have previously reported 3 cases of right ventricular stenosis which appeared to originate in this manner. More recently, this evidence has been challenged and theoretic objections have been raised as to the possible existence of the syndrome. The present report attempts to answer these contrary assertions and records another instance in which the syndrome was diagnosed clinically and confirmed at autopsy.

When systemic venous engorgement occurs in the hypertensive or arteriosclerotic subject, it is presumed that the right ventricle, having been unable to withstand the burden imposed by left ventricular insufficiency, has dilated and failed. In 1908, however, Bernheim first called attention to a striking anatomic paradox in which stenosis rather than dilatation of the right ventricle was found in patients who had died with the classic symptomatology of right-sided heart failure. In these patients, partial occlusion of the right ventricular cavity had resulted from deviation of a greatly hypertrophied interventricular septum which in some instances almost approximated the lateral wall of this chamber. The logical conclusion reached by Bernheim was that massive hypertrophy and dilatation of the left ventricle had been responsible for this unusual intrusion of the septum into the cavity of the right ventricle.

In subsequent publications in 1910 and 1915, Bernheim[1, 2] stressed the clinical aspects of the syndrome which has since borne his name. He emphasized that stenosis of the right ventricle should be considered when a patient with left ventricular hypertrophy presents the symptoms of right-sided heart failure in the absence of dyspnea and pulmonary congestion. The clinical picture of right-sided heart failure which is neither preceded nor accompanied by symptoms of left ventricular insufficiency should, therefore, suggest the diagnosis when significant hypertrophy of the left ventricle coexists.

Employing these criteria, numerous case reports have appeared in the French, Italian, Spanish, and Latin American literature. Over thirty publications by various authors[3–35] have supported the original observations and conclusions of Bernheim. Until recently, however, the syndrome attracted little attention from physicians in this country. Fishberg[36] has stated that the findings which he has observed in many necropsies have been in accord with Bernheim's views. White,[37] on the other hand, has expressed doubt on theoretic grounds as to the occurrence of this complex as a clinical entity. Glushein and Geer[38] in 1944 reported a case which they regarded as an example of this syndrome but the evolution of symptoms in their patient was quite the reverse of the sequence described as characterizing right ventricular stenosis. In 1945, the writers[39] reviewed the previous literature on the subject and reported 3 of their own cases which conformed closely to the criteria set forth by Bernheim. In 2 of these patients, both of whom had suffered from hypertensive heart disease, the diagnosis was made during life and confirmed at necropsy. In the third, the condition was discovered unexpectedly at postmortem examination when it was found in association with marked calcareous aortic and mitral stenosis.

Recently, however, Evans and White[40] after critical analysis of our protocols have controverted the evidence upon which the diagnosis of Bernheim's syndrome was made. They contend that other conditions such as pulmonary embolism or mitral stenosis may have been

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responsible for the appearance of right-sided heart failure in the absence of left-sided heart failure. Actually, however, pulmonary embolism could not have played a significant role in the symptomatology of our cases since it developed only in the terminal phase of the disease long after the appearance of systemic venous engorgement. Furthermore, to support the contention of these authors one would have to explain how mitral stenosis or pulmonary embolism, severe enough to cause chronic congestive failure, could be associated with a greatly reduced right ventricular cavity.

These authors have pointed out quite significantly that in the autopsy statistics of 2 of our subjects the liver weights were 850 grams and 1,100 grams and that these findings did not appear to indicate passive congestion. On rechecking the pathologist's report it was found that the former figure should have been 1,850 grams instead of 850 grams. The liver weight of 1,110 grams in the second instance (Case 1) was, however, an accurate measure of this organ in a small subject who was less than 5 feet tall. Atrophy and fibrosis as a result of chronic passive congestion also contributed to the relatively small weight of the liver. The microscopic appearance of this organ as reported by the pathologist (Dr. Lawrence Sophian) was typical of "cardiac cirrhosis."

Evans and White have also stressed the importance of the relative weights of the lungs and the liver in providing a clue as to whether or not peripheral congestion had been present without pulmonary congestion. Inasmuch as left ventricular failure and pulmonary engorgement frequently develop in the final days or weeks before death in patients with Bernheim's syndrome, this index would certainly not appear to be reliable. The presence of "cardiac cirrhosis," as in the case described above, would also tend to invalidate this criterion.

These authors carefully searched a group of 22 patients with massive left ventricular hypertrophy for examples of this syndrome. From their negative findings in this small series they expressed strong doubt as to the existence of the Bernheim complex. By analogy, one might ask whether an analysis of 22 patients with rheumatic mitral valvulitis in whom *Streptococcus viridans* vegetations were not found, would justify the conclusion that subacute bacterial endocarditis does not exist. In addition to the two reports which Evans and White have reviewed, there are over thirty published articles in foreign languages which support the original observations of Bernheim. Inasmuch as the former authors recommend that the designation "Bernheim's syndrome" be dropped "unless proof can be adduced to support it," we wish to present additional proof in the report of another case which we consider to fulfill even some of the rigid requirements set up by these critical observers.

Case Report

M. P., a 45 year old Portuguese white man was admitted to the hospital on April 9, 1945, with the complaint of swelling of the ankles, dizziness, and headaches of two weeks' duration. Past history revealed left inguinal hernioplasty in 1920 and surgery for peptic ulcer in 1928.

Physical examination showed a well-developed white man whose complexion was of a peculiarly dusky hue. The lips and nail beds were moderately cyanotic. There was no dyspnea. The cervical veins were distended. Funduscopic examination revealed marked narrowing and tortuosity of arterioles with arteriovenous nicking. The discs were pale. Temperature was 98 F., pulse rate 88, and respiration rate 20. The radial pulses were of good volume, equal, and regular. The blood pressure was 206/124. The heart was considerably enlarged, its left border being percussed in the anterior axillary line. There was a normal sinus rhythm. A soft, blowing systolic murmur was heard at the mitral area. The second aortic sound was increased in intensity and was considerably louder than the second pulmonic sound. The lungs were resonant throughout, the breath sounds were vesicular in type, and there were no râles. The liver border was 3 fingerbreadths below the right costal margin in the midclavicular line. The edge of the spleen was palpated on deep inspiration. There was marked pitting edema of the ankles. Venous pressure was 180 mm. of water. The arm-to-tongue circulation time was 25 seconds (decholin). Roentgenogram of the heart (fig. 1) showed a hypertensive type of configuration with moderate enlargement of the left ventricle and *clear* lung fields. The aorta was tortuous and moderately widened. There was a moderate increase in the perihilar bronchovascular markings and a small density in the left costophrenic angle due to thickened pleura. The electrocardiogram showed a normal sinus rhythm with a ventricular rate of 86; P-R interval 0.17 second; QRS interval 0.06 second; inversion of the T waves in Leads I, II,

and IV; low-voltage T waves in Lead III; and left axis deviation. Urinalysis revealed a specific gravity of 1.010 with marked albuminuria, occasional granular casts, and occasional red blood cells. Mosenthal test showed a fixed specific gravity around 1.010. The blood picture revealed a normal white cell count. There were 3,600,000 red blood cells and 70 per cent hemoglobin. The nonprotein nitrogen of the blood was 120 mg. per 100 cc.; the total serum protein was 6.2 grams, albumin 3.3 grams, and globulin 2.9 grams per 100 cubic centimeters. Blood Mazzini and Kahn reactions were negative.

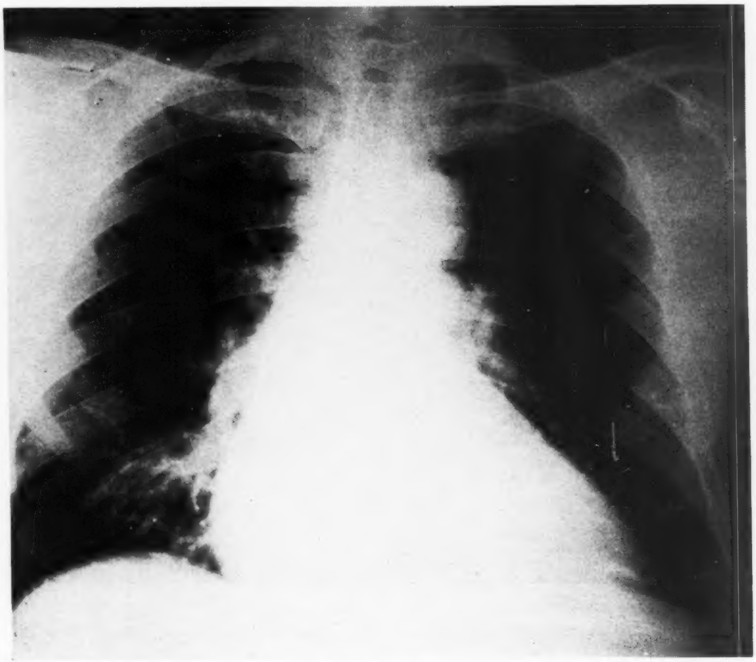

FIG. 1.—Roentgenogram showing considerable enlargement of the heart. Note minimal pulmonary congestion.

The patient was treated with rest in bed, digitalization, and an occasional injection of mercupurin. He was placed on a high-vitamin, low-salt diet and showed slow improvement. At all times during this hospitalization he was able to lie flat in bed without dyspnea. He continued to manifest a variable degree of cyanosis, liver enlargement, and ankle edema without pulmonary findings until his discharge on October 8, 1945. At that time he was ambulant and experienced dyspnea only on moderate exertion. The peculiar dusky grayish hue of the skin had persisted from the time of admission. A diagnosis of Bernheim's syndrome was made.

The patient was readmitted to the hospital on November 13, 1945, at which time he was found to be markedly dyspneic and cyanotic. Temperature was 98.6 F., pulse rate 110, and respiration rate 28. The blood pressure was 210/140. The cervical veins were markedly engorged. The cardiac findings were as previously noted except for a more rapid rate. The second pulmonic sound was equal to the second aortic, both being considerably increased in intensity. The liver border was palpated 4 fingerbreadths below the right costal margin in the midclavicular line. There was marked edema of the lower extremities. The nonprotein nitrogen of the blood was 236 mg. per 100 cubic centimeters. The patient failed to respond to oxygen, aminophylline, and other supportive therapy and finally expired on the third day of his second hospital admission. An autopsy was performed.

Autopsy Findings. The body was that of a normally developed and fairly well nourished adult man. There was no icterus or petechiae. There was pitting edema of the ankles and legs. The head was of symmetrical contour. The mouth showed cyanotic mucous membranes. The abdomen was distended and showed a healed left rectus incision.

The peritoneal cavity contained about 100 cc. of straw-colored fluid. The liver edge was 4 fingerbreadths below the costal margin. There was a posterior gastrojejunostomy whose stoma was functional. The pleural cavities showed smooth surfaces. There was about 50 cc. of straw-colored fluid in the

right side of the chest and about 100 cc. in the left. The pericardial cavity was completely obliterated; stringy fibrous bands produced adherence of the parietal to the visceral layers. The heart weighed 750 grams. There was marked prominence of the left ventricle. A cross section through both ventricles revealed concentric hypertrophy and dilatation of the left ventricular myocardium and interventricular septum. The latter was crescentic in shape, its convex surface infringing upon the right ventricle and markedly reducing the volume of that chamber (fig. 2). The myocardium was reddish brown and firm. Its measurements were as follows: left ventricle, 24 mm.; interventricular septum, 22 mm. anteriorly, 15 mm. at its midpoint, and 20 mm. posteriorly; right ventricle, 5 mm. The valves had smooth surfaces except for a few yellow atheromatous plaques in the anterior mitral leaflet. The chordae tendineae were thin. Measurements of the various valve rings were: pulmonic ring, 9.2 cm.; aortic ring, 7.8 cm.; tricuspid ring, 12.2 cm.; mitral ring, 13 cm. Both atria were dilated and their endocardium was smooth. The coronary ostia were patent and the arteries presented a smooth intimal surface. The right lung weighed 640 grams and the left 540 grams. The lung surfaces were smooth. There was no exudate. On section the tissue was doughy and contained air in all portions. On gentle pressure a slight amount of edema fluid extruded from both lower lobes. The liver weighed 2110 grams (this being almost twice the combined weight of the lungs). Its surface was smooth and texture firm. The color was brown with scattered yellow mottling. The spleen weighed 170 grams.

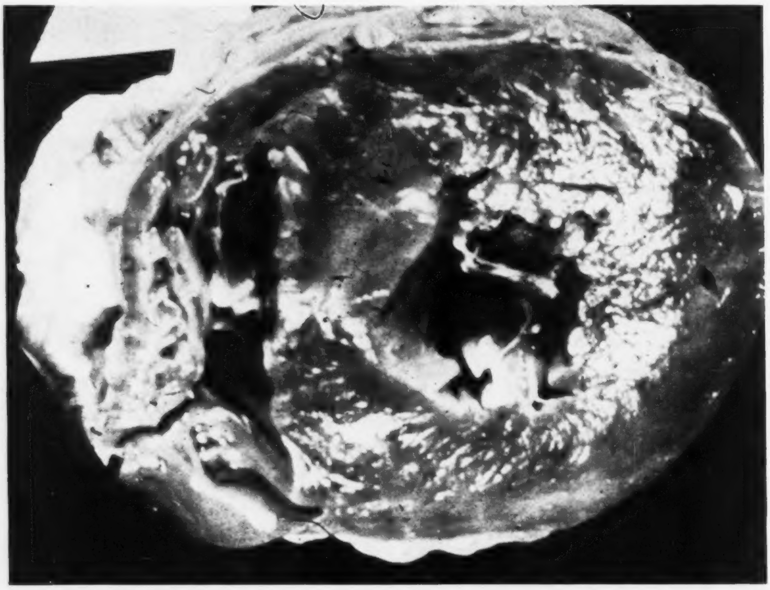

Fig. 2.—Transverse section of heart (midway between apex and base) showing marked left ventricular hypertrophy. The cavity of the right ventricle is greatly reduced in size by the bulging interventricular septum.

Discussion

In spite of theoretic arguments presented by some authors, the syndrome of Bernheim appears to be a definite clinicopathologic entity. Although the writers have studied the hearts in a large number of subjects with left ventricular hypertrophy who have been examined at autopsy, they have never observed the anatomic characteristics of the Bernheim complex in patients who presented the classic symptomatology of dyspnea and pulmonary congestion followed by systemic venous engorgement. Conversely, utilizing the clinical criteria of Bernheim, the diagnosis of the syndrome has not been made by us on any occasion in which confirmation was lacking at post-mortem examination.

The clinical picture of "isolated right-sided

heart failure" in association with appreciable left ventricular hypertrophy suggested the diagnosis in the case presented and in 2 of 3 previously reported cases observed by the writers. In all 3 of these patients the typical anatomic features described by Bernheim were found at necropsy. In a fourth case, almost complete obliteration of the apical portion of the right ventricle was unexpectedly found at autopsy in a patient with mitral and aortic stenosis of marked degree. The paradoxic association of mitral stenosis with a greatly reduced right ventricular cavity was readily explained by consideration of the accompanying findings. Thus, coexisting left ventricular hypertrophy and dilatation arising from aortic stenosis had caused an unusual intrusion of the hypertrophied interventricular septum into the cavity of the right ventricle. This phenomenon resulted in a virtual tricuspid stenosis which was manifested clinically by massive anasarca in association with unusually clear lung fields.

Evans and White have stated that the relative weights of the lungs and liver should give an indication of the degree of failure in the pulmonary and systemic circulations during life. In their opinion, if Bernheim's syndrome did exist, the combined weight of the lungs at autopsy in such a case would be within normal limits (900 to 1280 grams) while that of the liver would appreciably exceed its normal weight (1,440 to 1,680 grams) as well as that of the lungs. This was actually so in the case herein presented. Thus, the combined weight of the lungs was 1,180 grams while the weight of the liver was 2,110 grams (almost twice that of the lungs). As we have already pointed out, however, this index may often be misleading because of (1) the frequent advent of pulmonary congestion in the terminal days or weeks of the disease and (2) the occasional occurrence of "cardiac cirrhosis" of the liver in such cases of long-standing chronic passive congestion.

The evolution of right ventricular stenosis as found in the syndrome of Bernheim may be considered to have two distinct periods. In the first or anatomic period, there are few or no important clinical signs. Interference with the filling of the right ventricle is counterbalanced by dilatation of the infundibular portion of the chamber and by enlargement of the right auricle. There may be some distention of the cervical veins and the venous pressure may be found elevated while the circulation time remains at the upper limit of normal. The second, or clinical, period is divided into two stages. In the first stage there is "dissociated" failure of the circulation, that is, systemic venous engorgement without disturbance in pulmonary blood flow. The lung bases are clear and dyspnea is absent or minimal, while hepatic enlargement, ascites, and dependent edema may be marked. During this interval, the circulation time may still be within upper normal limits or slightly increased while there is appreciable elevation in venous pressure. Fluoroscopic and kymographic studies may establish enlargement of the left ventricle and right auricle, with normal size of the two other chambers, but we have not found these procedures of much assistance in diagnosis. It is this stage of "isolated right-sided heart failure" which is recognizable clinically as Bernheim's syndrome. In the second stage which represents total failure of the heart disturbance of the lesser circulation is added to the earlier symptoms of venous obstruction. At this time, therefore, when dyspnea and orthopnea become evident, the resulting clinical picture can no longer be distinguished from that in the usual type of combined left and right ventricular failure.

Our autopsy material clearly demonstrates the striking disproportion between the left and right ventricles in these cases. The findings seem particularly significant when it is realized that the degree of right ventricular stenosis during life is probably even greater than that actually found at necropsy. This is explained by the fact that dilatation of the pulmonary conus and base of the right ventricle develops as a terminal event when left ventricular failure finally supervenes.

Summary and Conclusions

1. In spite of arguments to the contrary, there is already sufficient proof in the literature to justify acceptance of Bernheim's syndrome as a clinical entity.

2. The diagnosis is suggested when a patient with left ventricular hypertrophy shows signs of right-sided heart failure as the first indication of circulatory embarrassment, i.e., systemic venous engorgement without pulmonary congestion.

3. This picture of "isolated right-sided heart failure" is the result of stenosis of the cavity of the right ventricle through displacement of the interventricular septum due to marked enlargement of the left ventricle. The degree of right ventricular occlusion is probably even greater than that demonstrable at autopsy.

4. Clinically, dyspnea and other signs of pulmonary congestion are conspicuously absent or minimal until the terminal stage of the disease when failure of the left ventricle finally supervenes.

5. A case showing the typical clinical and anatomic features of right ventricular stenosis which was diagnosed during life and confirmed at necropsy is presented. Reference is also made to 3 cases previously reported by the authors in which the Bernheim complex was observed.

6. The theoretic objections advanced by others against the possible existence of this clinicopathologic syndrome appear to be unfounded.

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Rupture of a Papillary Muscle of the Heart; Report of Two Cases

By John Chandler Smith, M.D.

The paper presents clinical and pathological data on 33 cases of ruptured papillary muscle of the heart as revealed by review of the literature. All of the known causes of this event are listed and the characteristic clinical features are emphasized by including two additional typical case reports.

According to Stevenson and Turner,[1] the first case of rupture of a papillary muscle of the heart was reported by Merat in 1803. Since then only 33 cases have been reported and all but 2 of these reports have been recently summarized in a review of the literature by Davison.[2] Davison found 3 instances of papillary muscle rupture in 14,000 autopsy subjects examined at the Mount Sinai Hospital in New York City. Stevenson and Turner[1] found 2 such cases in 6,000 autopsy subjects examined at the Johns Hopkins Hospital in Baltimore. Review of 10,500 autopsies recorded at the Institute of Pathology, University Hospitals of Cleveland, revealed one case of papillary muscle rupture. This is one of the cases reported in this article. The second case is taken from the autopsy records of the Department of Pathology of Cleveland City Hospital.

Case Reports

Case. 1—The patient was an Italian laborer, 56 years old, who was well until November, 1937. At this time he experienced nonradiating severe substernal chest pain of sudden onset and pronounced shortness of breath. There were moderate cyanosis and râles throughout both lungs. The patient remained in bed for one week following the onset of symptoms. Thereafter, he complained of no symptoms and was able to do light work. On February 21, 1938, he suddenly experienced extreme shortness of breath accompanied by a sense of marked apprehension. He was put to bed and his condition did not change until the next morning when he complained of pain in the left arm. By 7:00 P.M. he had become comatose. He was admitted to University Hospitals of Cleveland at noon on February 23, 1938.

Physical examination revealed a well-developed, comatose white man who was markedly cyanotic, perspiring profusely, and breathing rapidly. The temperature was 40 C., the pulse rate 158, and the respiration rate 44. The blood pressure was 110/92. Auscultation of the chest revealed stertorous breath sounds, and fine râles were present over the posterior bases of the lungs. Percussion revealed the left border of cardiac dullness to extend 12 cm. from the midsternal line in the sixth intercostal space. The heart beat was rapid and regular. A harsh systolic murmur was present over the apex of the heart and was somewhat obscured by the breath sounds. The abdomen was soft and no masses were palpated. The remainder of the physical examination revealed no abnormalities.

Hematologic examination revealed 19.6 grams of hemoglobin. There were 6,700,000 erythrocytes and 18,000 leukocytes per cu. mm. of blood. Differential count of 100 cells revealed 70 segmented granulocytes, 18 band cells, 10 lymphocytes, and 2 monocytes. The urine was brown, clear, and contained a trace of albumin. The blood Wassermann reaction was negative. An electrocardiogram made on the day of admission was thought to give evidence of a recent and old infarct of the posterior wall of the left ventricle.

The patient was promptly placed in an oxygen tent but remained unconscious. By 3:00 P.M. on the day of admission the pulse and blood pressure were unobtainable. Gasping, labored respirations developed and the patient died at 2:00 A.M. on February 24, 1938.

Autopsy Report (6118): The heart weighed 500 grams. The epicardium was smooth and transparent except over the posterior surface of the left ventricle at the apex where a region measuring approximately 5 by 3 cm. was discolored gray and slightly roughened by fibrous tags. The underlying myocardium was grayish white and thin, measuring, in one region, 8 mm. in thickness. A narrow zone of muscle at the periphery of this region was soft and discolored dark purplish-red. Elsewhere the myocardium was moderately firm and light brownish red throughout. The left posterior papillary muscle arose from the center of the thin portion of the ventricle

From the Institute of Pathology, Western Reserve University Hospitals, Cleveland, Ohio.

and was completely separated in its midportion by an irregular laceration. The surface of the segment arising from the ventricular wall was covered by a grayish-brown mural thrombus. The free portion was attached to the posterior mitral leaflet by twisted chordae tendineae which drew the muscle segment close to the free margin of the valve (fig. 1).

Branches of the right coronary artery extended down the interventricular groove and over the posterior wall of the left ventricle. Transverse sections of the right coronary artery at the acute margin of the heart revealed a large lumen occluded, except for minute central openings, for a distance of 1.5 cm., by firm gray tissue. Distal to this region the lumen was occluded for a distance of 1 cm. by a recent thrombus that was red mottled with brown. Transverse section of the left coronary artery revealed a patent lumen moderately narrowed by focal yellowish-gray intimal plaques.

The other pertinent gross diagnoses included bronchopneumonia, recent infarcts of the right and left kidneys, old infarct of the spleen, and moderate arteriolar nephrosclerosis. The gross diagnoses were confirmed by microscopic examination.

Comment: The stertorous character of the respirations was thought to obscure partially the harsh apical systolic murmur characteristic of ruptured papillary muscle.

Case 2.—The patient, a white laborer, 58 years old, was well until February 6, 1948, when he first experienced pain in the left side of his chest. The pain was of abrupt onset and radiated to the left shoulder, arm, and hand. It was intermittent and of about thirty minutes' duration with recurrence every three to four hours for the following three days. At 11:00 P.M. on February 9, 1948, the patient suddenly experienced a constant and severe substernal squeezing sensation associated with aching and numbness of the left arm and hand. He perspired freely, vomited several times, and became cold and apprehensive. He was admitted to Cleveland City Hospital at 2:00 A.M. on February 10, 1948, in a state of collapse.

FIG. 1.—The ruptured posterior papillary muscle and underlying myocardial infarct of Patient 1.

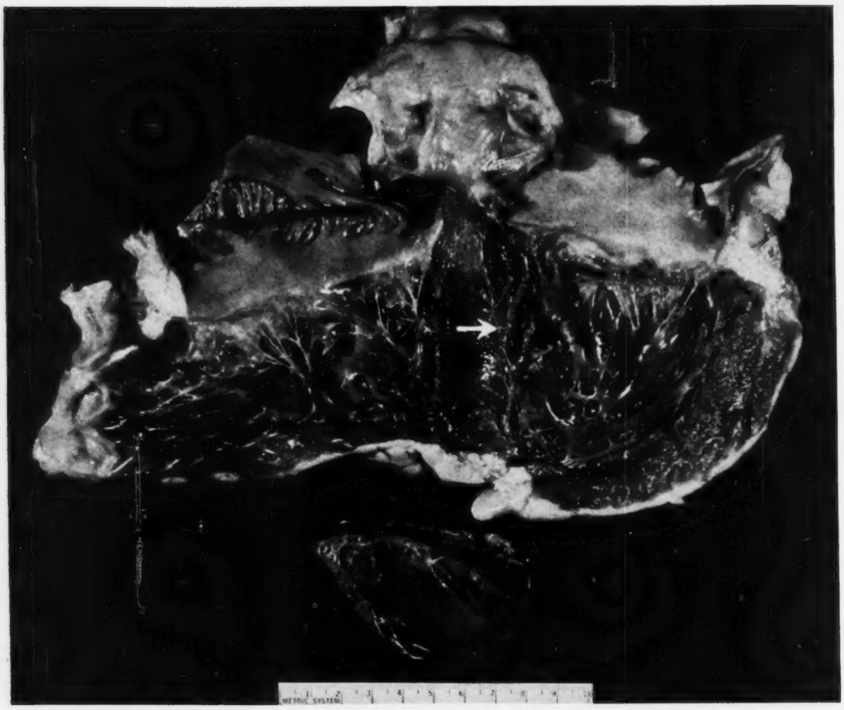

FIG. 2.—The heart of Patient 2 opened for injection study of the coronary arteries shows rupture of the posterior papillary muscle of the left ventricle.

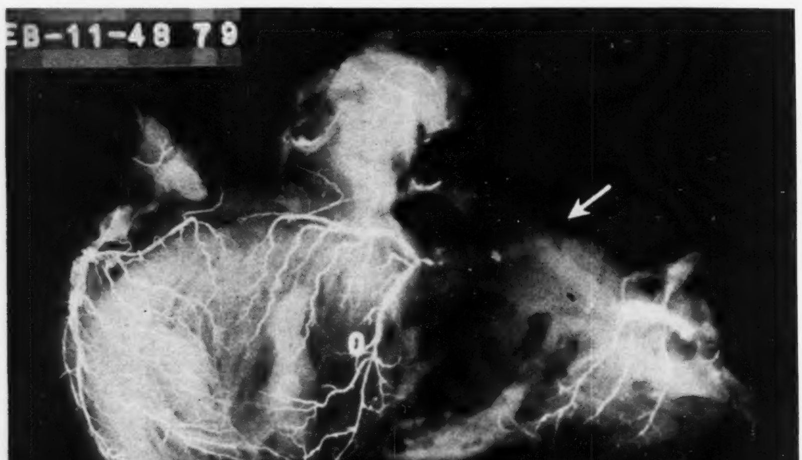

FIG. 3.—Roentgenogram of the heart of Patient 2 after injection of the coronary arteries with radio-opaque latex. An extensive thrombus occludes the lumen of the right coronary artery. (Appreciation is extended to Dr. Arthur Young for preparation of figure 3 and permission for its publication in this report.)

The pulse rate was 120, respiration rate 28, temperature 37.2 C., and blood pressure 80/50. Physical examination revealed an acutely ill white man who was apprehensive, pale, and slightly cyanotic. Examination of the heart revealed no enlargement. Although the cardiac sounds were barely audible, the rhythm was regular and a soft systolic murmur was heard over the apex of the heart. The lungs were clear to auscultation and percussion. The abdomen was soft and nontender. The remainder of the physical examination revealed no abnormality.

Hematologic examination revealed 12 grams of hemoglobin. There were 5,200,000 erythrocytes and 21,000 leukocytes per cu. mm. of blood. Differential count of 100 cells disclosed 84 segmented granulocytes, 14 lymphocytes, and 2 monocytes. Urinalysis was not remarkable.

Soon after admission the blood pressure dropped to 60/30 and then became unobtainable. The patient continued to vomit and died approximately one hour after entering the hospital.

Autopsy Record (17386): The heart weighed 420 grams. Palpation revealed a region of softening over the posterior wall of the left ventricle extending from the apex at its junction with the interventricular septum to within 4 cm. of the base. Section disclosed a light brownish-red, moderately firm myocardium except in the region of softening where the cut surface was dark brownish-red and dull. The posterior papillary muscle of the left ventricle arose from the center of the region of softening and was completely separated in its midportion by a ragged oblique laceration (fig. 2). The free segment was held to the mural endocardium by a short tendinous cord. A branch of the right coronary artery formed the posterior descending vessel. Transverse sections of the right coronary artery disclosed a large lumen completely occluded 4 cm. from its orifice by a firm, mottled, dark-red and gray thrombus that extended for 6 cm. along the course of the vessel (fig. 3). Transverse sections of the anterior descending and circumflex branches of the left coronary artery revealed the lumens of the first portion of each to be markedly stenotic because of yellowish-gray intramural deposits that cut with calcific hardness.

Histologic examination revealed a recent thrombus of the right coronary artery, marked arteriosclerosis with stenosis of the left coronary artery, recent infarcts of the posterior wall of the left ventricle, focal fibrosis of the anterior wall of the left ventricle, and marked passive hyperemia of the lungs.

Comment: The clinical manifestations of papillary muscle rupture were characteristic in that there was an abrupt increase in the severity of the angina and sudden onset of profound shock three days after the onset of the illness.

Discussion

Of the 33 reported cases of rupture of a papillary muscle, 18 were the result of thrombosis of a coronary artery with infarction of the myocardium.[2] The posterior papillary muscle of the left ventricle was ruptured in 13 of the subjects, in 11 of whom there was a thrombus of the right coronary artery or circumflex branch of the left coronary artery. In 2 patients with rupture of the left posterior papillary muscle the thrombus was in the anterior descending branch of the left coronary artery. Rupture of the anterior papillary muscle of the left ventricle resulted from coronary artery thrombosis in 5 patients, in 3 of whom the thrombus occluded the circumflex or anterior descending branch of the left coronary artery. In 2 patients with rupture of the left anterior papillary muscle the thrombus was in the right coronary artery.

In two cases, reported in the years 1824 and 1865,[1] there was rupture of a papillary muscle of the right ventricle. The first occurred in a white woman, 22 years old, with advanced pulmonary tuberculosis. Autopsy examination disclosed vegetations on the tricuspid valve leaflets, attached chordae tendineae, and ruptured papillary muscle. The second occurred in a white woman, 23 years old, who died seven weeks post partum with puerperal sepsis, peritonitis, and pneumonia. Autopsy disclosed vegetations on the leaflets of the tricuspid valve, attached chordae tendineae, and ruptured papillary muscle of the right ventricle.

There have been 2 cases reported, neither of which is included in the review by Davison, in which the papillary muscle rupture was caused by trauma. The patient reported by Glendy and White,[3] a white seaman, 24 years old, died twenty-six hours after being run over by a truck. Autopsy examination revealed a purplish-red contusion on the anterior surface of the left ventricle. There was no penetrating wound of the external surface of the heart. A hemorrhagic laceration separated the base of the left anterior papillary muscle from its ventricular attachment. The coronary arteries revealed no thromboses or extensive ruptures. There were also a fracture of the left eleventh rib, bilateral bronchopneumonia, and extensive hemorrhagic contusions of the thorax and abdomen. The patient of Payne and Hardy,[4] a white man 51 years old, was found

unconscious beside a moving conveyor belt which he had attempted to repair with a heavy stick. Death occurred approximately one hour later and autopsy examination revealed a fracture of the sternum and left third and fourth ribs and a contusion of the anterior wall of the left ventricle. The base of the left posterior papillary muscle was partially separated from the ventricular wall. The coronary arteries were intact and patent throughout.

One case, reported by Spaulding and Von Glahn,[5] was thought to be due to syphilis. The patient was a Negro, 31 years old, who died suddenly during a recurrent episode of congestive heart failure. The blood Wassermann reaction was four plus. Autopsy revealed the posterior papillary muscle of the left ventricle to be ruptured and microscopic examination of the stump is reported to have revealed a central focus of coagulative necrosis surrounded by a thin subendocardial zone of fibrosis in which a Levaditi preparation revealed spirochetes. The coronary arteries were patent and the myocardium of the ventricles was of normal consistency and color. In addition, there was syphilitic aortic valvulitis with aortic insufficiency.

One case referred to by Davison, report of which has not yet been published,[2] was thought to be due to polyarteritis nodosa. The patient was a white man, 57 years old, who died twenty-four hours after suddenly developing pulmonary edema. Examination disclosed a harsh systolic murmur. Autopsy examination revealed polyarteritis nodosa involving the heart, liver, and urinary bladder. There were multiple small hemorrhagic infarcts of the myocardium including that of the anterior papillary muscle of the left ventricle which was ruptured. The coronary arteries revealed slight arteriosclerosis but were patent throughout.

Of the 31 cases reported in which trauma was not the etiologic factor, a significant change in the patient's clinical condition indicating the probable time of papillary muscle rupture was described in 17.[2] In 10 of these patients, death occurred in less than nine hours after this clinical change and none lived more than thirty-six hours thereafter. Death occurred in less than fourteen days in all but 2 of the remaining patients in whom the time of papillary muscle rupture was not ascertained. One patient lived twenty-one days after the onset of symptoms and the patient of Merat, according to Stevenson and Turner,[1] lived twenty months after what was clinically thought to be the time of the papillary muscle rupture.

The clinical signs and symptoms preceding rupture of a papillary muscle are usually those of recent myocardial infarction. The rapidity with which death follows this event often precludes the clinical diagnosis. However, sudden increase in the severity of the angina, the appearance of a harsh apical systolic murmur, and profound shock suggest the diagnosis. Murmurs present before the rupture of the papillary muscle usually change in character and increase in intensity.[2] The antemortem diagnosis of papillary muscle rupture was considered in only one of the reported cases.[2]

The differential diagnosis includes rupture of the following structures: an aortic cusp, the interventricular septum, the ventricle, and the mitral chordae tendineae. Rupture of an aortic cusp is manifested by a high pulse pressure and the abrupt onset of a loud diastolic murmur over the aortic area.[6] Rupture of the interventricular septum is distinguished by a left atrium of normal size and a thrill and systolic murmur, most pronounced over the third or fourth intercostal space, that is transmitted chiefly to the right.[6] A large ventricular rupture causes sudden death. A small ventricular rupture may cause hemopericardium and cardiac tamponade manifested by a low pulse pressure and a small silent heart.[7] Rupture of the mitral chordae tendineae is usually antedated by bacterial endocarditis and rarely causes death within a short time. It is characterized by a harsh systolic and diastolic murmur and thrill of abrupt onset that is loudest over the apex of the heart.

Summary

The thirty-fourth and thirty-fifth case reports of rupture of a papillary muscle of the heart are presented. The reported causes of

this event are coronary thrombosis with myocardial infarction, trauma to the chest, and syphilis. One case, not yet reported, is supposed to have been due to polyarteritis nodosa. The diagnosis is suggested in a patient, exhibiting evidence of a recent myocardial infarct, who suddenly develops a pronounced increase in the severity of the chest pain associated with profound shock and who on examination reveals a harsh apical systolic murmur which was previously absent. Death usually occurs within twenty-four hours following rupture of a papillary muscle of the heart.

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Sarcoidosis of the Heart

A Cause of Sudden and Unexpected Death

By William E. Kulka, M.D.

Sarcoidosis (Benier–Boeck's disease) is not limited to skin or eye as once thought. Now it is known to be a chronic granuloma of the reticulo-endothelial system, dispersing tubercle-like nodes over all organs. Assumption of benignity had to be abandoned. Supporting proof that it can be the cause of death is this report of an autopsy of a young woman following sudden death due to extensive sarcoidosis of the heart, with miliary nodes scattered in most of the organs. No signs of tuberculosis could be found.

SARCOIDOSIS, or Besnier-Boeck-Schaumann's disease, has attracted the interests of the research worker as well as the clinician in an ever increasing degree during the last decade. From its status as a medical curiosity it has emerged as a more widely recognized and fairly well-defined entity. Its occurrence seems universal.[2]

What was first described as an interesting, although rare, disease of the skin by Besnier, in 1889, and independently by Boeck,[3] also in 1899, was later found in the eye and salivary glands and is now considered a systemic disease presenting the features of a chronic infectious granuloma. Like its counterpart, tuberculosis, it can invade every organ of the body as well as bone marrow, dura and the eye. The skin manifestations, although frequent, probably are not present in more than 20 per cent of all cases.[3]

The experiences of the last twenty years have stressed the fact that sarcoidosis is a general spreading disease with a predilection for the lympho-reticulo-endothelial and hematopoietic systems.[7] The assumption of the absolute benignity had to be abandoned when there were occasional reports of autopsies performed on patients who had died as a direct consequence of the disease. Even though one would wish to exclude caseating tuberculosis as a natural development of sarcoidosis[11] and limit the number of direct casualties to those who succumbed to direct effects of specific conditions, the refutation of the benignity stands. This observation was made by M. Pinner,[3, p. 92] in 1939, in a collective report of thirty-nine autopsies. Rubin and Pinner,[11] in 1944, described twenty-five autopsies with the same deduction. Reiser,[7,8] Rosenthal,[10] and Freimann[2] also arrived at the same conclusion. The latter author, up to 1948, had collected altogether seventy autopsied cases. He included nineteen from their own institution in Boston; the remainder were compiled from the literature. He stated that many of them were incompletely described or complicated by other diseases, chiefly tuberculosis and syphilis. In several the diagnosis was open to doubt.

Recognition of the damage caused by sarcoidosis in one specific focus, or its dissemination, was instigated by Longscope[5, 6] with his discussion of involvement of the heart. He added three autopsies of his own, one of which was complicated by syphilis. Apparently Cotter[1] was the first to present the extensive changes in the myocardium caused by these nodes found at autopsy which resembled tubercles but differed from tuberculosis. He reported the case of an 18 year old Negro who was observed clinically prior to his death. There was considerable anergy against tuberculin during life. The histologic findings post mortem of tubercle-like noncaseating nodes in the skin, spleen, lymph nodes and alimentary tract, as well as the extensive specific infiltration of the cardiac wall corroborated the diagnosis of sarcoidosis. The only complicating factor was a strongly positive Wassermann reaction. Another death due to widespread involvement of the heart by tubercle-like noncaseating nodes was re-

From the Cuyahoga County Coroner's Office, Cleveland, Ohio.

ported by Johnson and Jason[4] in 1946 (see addendum).

The paucity of reported autopsies on such cases[2] influenced the writer to publish the following case in which extensive damage to the myocardium due to sarcoidosis was found.

Case Report

History: A 26 year old Negro woman collapsed and expired suddenly on the street. Her sudden and unexplained death became a subject for the Coroner's investigation. A scant history was pieced together from information obtained from her husband and a physician who had seen her several times in the three months prior to death because of a complaint of chronic inflammatory condition within the pelvis. At the beginning of the treatment period this physician had noticed several nodes which resembled sarcoids on her arms, legs and cheek. These disappeared without medication. No biopsy was taken. There was no history of fever or chills. There was a history of some intermittent attacks of slight cardiac palpitation during the last few months prior to her death. She was never hospitalized. No electrocardiogram was taken. Urine examination and serology were negative. There were no microscopic or chemical examinations of the blood. Late x-ray films of the chest showed some blurred increase in the mediastinal lymph nodes. The deceased was not engaged in factory work or otherwise gainfully employed.

Abstract of Autopsy Findings: The body is that of a colored female 66 inches tall and weighing 132 pounds. The skull and brain show no abnormalities.

Lymph Nodes: The cervical and axillary lymph nodes are not enlarged. There are clusters of enlarged grayish red and moderately soft lymph nodes along both sides of the trachea, at its bifurcation and along the main bronchi. Some of them are matted together. On cross section, these lymph nodes are grayish red. Where matted together the outlines of the individual lymph nodes are distinctly visible. The mesenteric lymph nodes show no gross abnormalities. There is, however, a number of retroperitoneal lymph nodes along the abdominal aorta from the hiatus of the diaphragm to the bifurcation of the aorta, which are moderately enlarged and yellowish or grayish pink on cross section.

Spleen: The spleen weighs 250 grams and is dark red and congested. On cross section the follicles appear irregularly enlarged.

Pericardial Sac and Heart: There is about 30 cc. of clear fluid in the pericardial sac. The heart is moderately enlarged, weighing 300 grams. The right ventricle is markedly dilated and its walls thinned. There are large areas of white discoloration at the anterior and posterior wall of the left ventricle. On cross section, more than half of the lower portion of the left ventricle, including septum and apex as well as both papillary muscles, appears yellowish white and glistening (fig. 1). The rest of the cardiac musculature is light grayish red. All the valves are free and tender. The epicardium outside of the dull whitish area is smooth. The coronary arteries are patent and elastic but the left lateral limbs of the anterior descending branch of the left coronary artery leading into the whitish area described above seem to be somewhat compressed and narrowed. Aorta and pulmonary artery show no marked abnormality.

The gastrointestinal tract, liver, pancreas and kidneys are of normal appearance. There are bilateral parametrial adhesions and a moderate degree

Fig. 1. Opened left cardiac ventricle. Note whitish discoloration of papillary muscles and of lower part of cardiac wall

of hydrosalpinx. The menstruating uterus is of medium size.

There are no gross abnormalities of the endocrine glands including the persistent thymus.

Histologic Findings:

Mediastinal, paratracheal and some of the retroperitoneal lymph nodes in the bifurcation of the diaphragm: Many of the lymphoid follicles are replaced by nodes consisting of a fibrous capsule rich in collagen which surrounds groups of epitheloid (reticulo-endothelial) cells and one or several multinucleated giant cells. The darkly staining nuclei in these giant cells, twenty or more, are arranged in clusters or in the periphery of the slightly acidophilic cytoplasm. Some of these nodes are surrounded by lymphoid cells, but there is a striking absence of eosinophile or polynuclear neutrophile leukocytes.

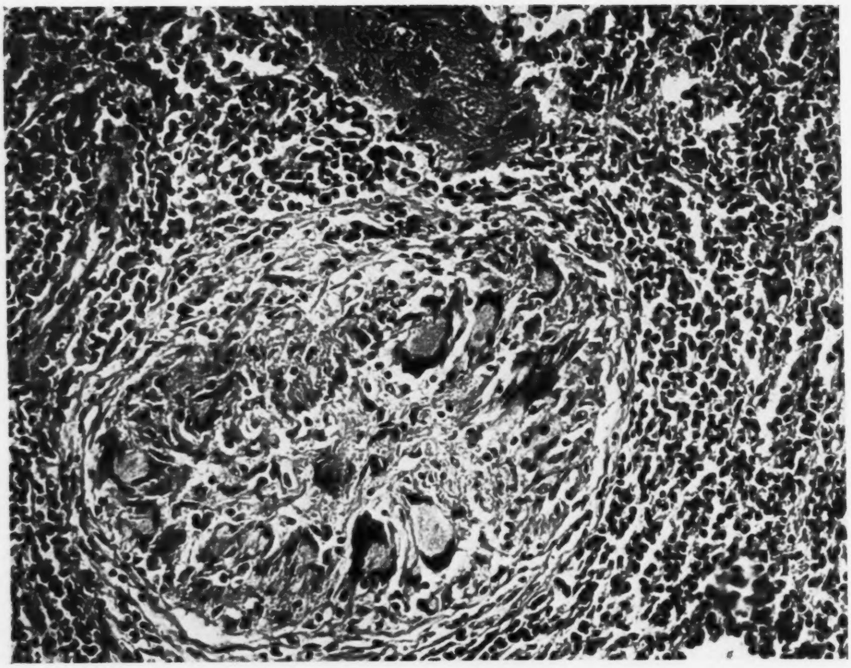

FIG. 2.—Sarcoidosis of spleen

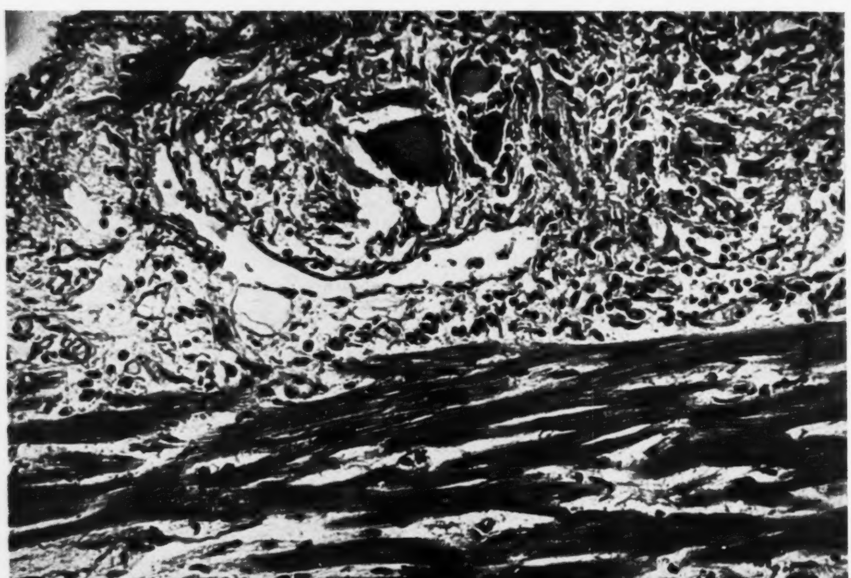

FIG. 3.—Sarcoidosis in left cardiac wall infiltrating the cardiac musculature

Some increased fibrosis with a scarlike density may appear in some of the larger lymph nodes. However, nowhere is the fibrous capsule penetrated.

Spleen: Among the normal looking lymphoid follicles are many tubercle-like nodes of the character described above (fig. 2).

Heart: Sections taken from the whitish areas of the left ventricle show that most of the cardiac musculature is replaced by a network of fibroblasts, which enclose multiple tubercle-like nodes with many polynuclear giant cells. A number of nodes are fused together. In some places where the fibrosis of stroma is increased, the number of typical nodes is decreased. In the periphery of the granuloma, where bundles of muscle fibers remain, clusters and columns of mononuclear white cells can be seen infiltrating the interstitial tissue. The corresponding epicardium presents multiple perivascularly arranged tubercle-like nodes in the subepicardial layers (figs. 3 and 4). Right Ventricle: Only a few scattered nodes are seen in the epicardium and between the cardiac muscle fibers.

Lungs: A number of small tubercle-like nodes are present in the perivascular connective tissue but there is no fibrosis or necrosis.

A few characteristic nodes are seen in the gastric mucosa, liver, kidneys, thyroid, adrenals and pituitary gland.

There are no specific changes in blood or bone marrow.

Silver stains of tubercles in lymph nodes and in the affected area of the heart revealed a delicate network of fibrils.

Specific stains failed to reveal the presence of any characteristic organisms.

Diagnosis: The cause of death was acute cardiac failure in a case of generalized sarcoidosis with extensive specific infiltration of the wall of the left ventricle of the heart.

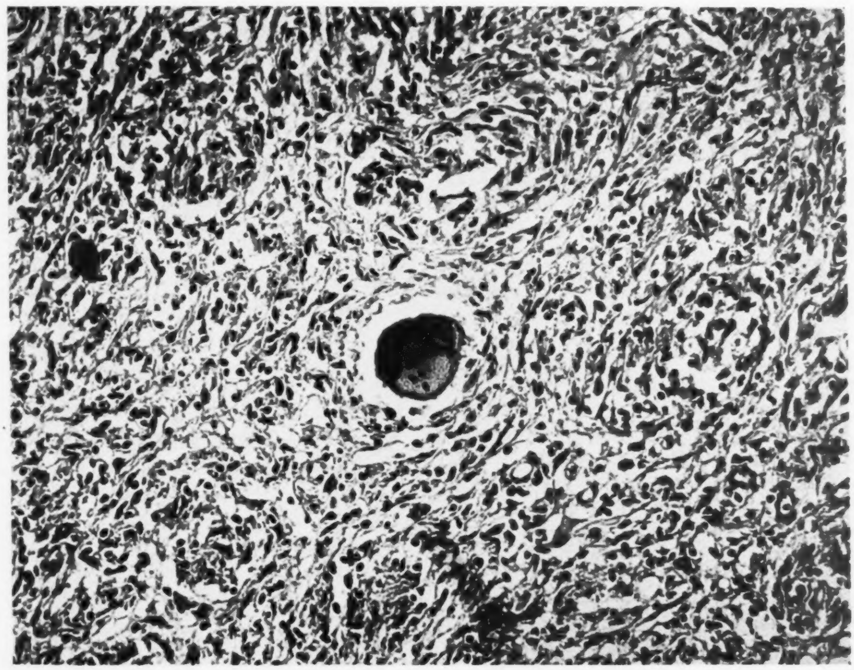

FIG. 4.—Typical polynuclear giant cell in reticular stroma (left cardiac ventricle)

DISCUSSION

A classic picture of sarcoidosis is delineated by (1) the simultaneous spread of tubercle-like nodes of granulomatous tissue formed by epitheloid and reticulo-endothelial cells enclosing the typical multinucleated giant cells, (2) the absence of eosinophiles, in contradistinction to Hodgkin's disease, (3) the absence of polynuclear neutrophiles, i.e., lack of evidence of acute inflammation, (4) the absence of caseating necrosis and (5) the minimal amount of fibrosis.

Remarkable in this case is the simultaneous dissemination through the organs and the

lympho-endothelial system with a semblance of the spread of miliary tuberculosis. However, there is no reckless destruction of the organ parenchyma. Where reticulo-endothelial tissue was involved, in some instances, an increased degree of fibrosis resulted.

Attention is called to the fact that in many sites the presence of the nodes was discovered only by means of microscopic examination. Many such nodes may heal and disappear with no remaining evidence or sometimes leaving only a non-specific scar. In this particular case an exception is seen in the extensive destruction in the heart muscle described above. Often this was a result not only of the confluence of the tubercle-like nodes but also of a fibrosis or a widespread infiltration by reticulo-endothelial and lymphoid-like cells causing atrophy of the cardiac musculature. It seems worthy of mention that where normal heart muscle and sarcoid tissue meet in the left ventricle one can see the invasion of the former by finger-like processes.

Progressive decrease in the efficiency of the left ventricle was followed by acute dilatation and subsequent failure of the right ventricle due to the overload. The marked involvement of the epicardium and the specific perivascular localization of the granulomatous process hastened the failure. There was no increased resistance to the pulmonary circulation due to massive infiltration or interstitial fibrosis of the lungs, which has been mentioned as one cause of death in sarcoidosis of the heart.[2, 8] The destruction in this case was so widespread as to cause the myocardial failure in contradistinction to the assumption of a specific interference with the cardiac conductive system described by Longscope.[5, 6, 9]

This case is distinguished by the fact that it was not influenced by additive effect of such complications as manifest tuberculosis or syphilis. This absence of tuberculosis seems remarkable, since the study of the literature leads one to parody Ewing's expression for the association of Hodgkin's disease and tuberculosis, i.e., we might say: "Tuberculosis follows sarcoidosis like a shadow."

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Summary

An autopsy performed on a 26 year old Negro woman who died suddenly and unexpectedly is reported.

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Sarcoid nodes were found disseminated in the lungs, mediastinal and retroperitoneal lymph nodes, spleen, gastric mucosa, liver, kidney, thyroid and pituitary glands.

The case was free of evidence of tuberculosis or syphilis.

Addendum

An additional case of sarcoidosis of the myocardium was reported recently in a clinicopathologic review of 300 cases of sarcoidosis compiled by Ricker and Clark.[9]

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A Case of Marked Dilatation of the Pulmonary Arterial Tree Associated with Mitral Stenosis

By S. Segall, M.D., I. I. Ritter, M.D., and W. Hwang, M.D.

A case which was studied with the technic of catheterization is discussed as a problem in the diagnosis of this syndrome.

A CASE of marked dilatation of the entire pulmonary arterial tree with calcification is being reported because of the rarity of the condition, and the unusual roentgenologic and clinical findings. The patient has been followed at the Michael Reese Hospital for a number of years. Intracardiac catheterization was recently performed in an attempt to arrive at a more accurate diagnosis, and to determine, if possible, what primary etiologic factors were involved.

Case Report

Mrs. A. C., a 42 year old housewife, was admitted to the Michael Reese Hospital on November 27, 1948, with minor lacerations and bruising following an automobile accident. Her father had died of pneumonia, and her mother of a heart attack at the age of 42 years. As a child her development was normal, and she enjoyed fairly good health. At the age of 14 years her tonsils were removed. Signs of heart disease present at that time led to a diagnosis of mitral stenosis. At the age of 16 she developed acute rheumatic fever and spent eight months in bed. It was during this illness that cyanosis and clubbing of the fingers were first noted. After this episode, however, aside from slight dyspnea on exertion, she carried on fairly normally, and continued to work. She was married at the age of 24. During the next few years she had four miscarriages.

In March 1939 she spent six weeks in the hospital with pneumonia, and developed thrombophlebitis of the veins of the leg. Physical examination of the cardiovascular system at that time revealed a diffuse apical impulse in the sixth intercostal space at the anterior axillary line. The second pulmonic sound was accentuated. There was a systolic thrill and a harsh systolic murmur over the left border of the sternum, and a systolic and presystolic murmur at the apex. The liver and spleen were not palpable. There was slight ankle edema, cyanosis was present, and there was marked clubbing of the fingers.

In November 1939 a pregnancy was terminated because of the patient's cardiac lesion. One month later, following a cold and sore throat, she was readmitted to the hospital with fever, polyarthritis dyspnea, orthopnea, and cyanosis. She developed acute pericarditis with effusion and congestive failure. Her course was stormy requiring oxygen therapy, mercurial diuretics, and digitalization. After discharge from the hospital, dyspnea on walking persisted and ankle edema was now a frequent manifestation. In February 1943 she was again admitted to the hospital, this time for medical examination before undergoing extraction of a tooth. At that time her main complaints were frequent headaches, mild dyspnea on exertion, and occasional ankle edema. She had been taking digitalis steadily for three years. Physical examination revealed a well nourished, well developed cyanotic woman. There was marked clubbing of the fingers and toes. A malar flush was present. Her blood pressure was 140/90. A few moist râles were present at both lung bases. There was a systolic retraction of the lower end of the sternum. The apex beat was diffuse. The heart was enlarged to the left and downward to the sixth intercostal space just outside the midclavicular line. A systolic thrill was palpable in the third left intercostal space, lateral to the sternal border. The second pulmonic sound was very loud. There was a short, harsh systolic murmur at the apex with accentuation of the first sound. This was followed by a low-pitched, rumbling mid-diastolic murmur. A rough systolic murmur of a different quality was present over the left border of the sternum, best heard over the lower portion. The liver border was palpable 5 cm. below the right costal margin and pulsation was present. The spleen was not palpable.

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lympho-endothelial system with a semblance of the spread of miliary tuberculosis. However, there is no reckless destruction of the organ parenchyma. Where reticulo-endothelial tissue was involved, in some instances, an increased degree of fibrosis resulted.

Attention is called to the fact that in many sites the presence of the nodes was discovered only by means of microscopic examination. Many such nodes may heal and disappear with no remaining evidence or sometimes leaving only a non-specific scar. In this particular case an exception is seen in the extensive destruction in the heart muscle described above. Often this was a result not only of the confluence of the tubercle-like nodes but also of a fibrosis or a widespread infiltration by reticulo-endothelial and lymphoid-like cells causing atrophy of the cardiac musculature. It seems worthy of mention that where normal heart muscle and sarcoid tissue meet in the left ventricle one can see the invasion of the former by finger-like processes.

Progressive decrease in the efficiency of the left ventricle was followed by acute dilatation and subsequent failure of the right ventricle due to the overload. The marked involvement of the epicardium and the specific perivascular localization of the granulomatous process hastened the failure. There was no increased resistance to the pulmonary circulation due to massive infiltration or interstitial fibrosis of the lungs, which has been mentioned as one cause of death in sarcoidosis of the heart.[2, 8] The destruction in this case was so widespread as to cause the myocardial failure in contradistinction to the assumption of a specific interference with the cardiac conductive system described by Longscope.[5, 6, 9]

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There was slight pitting edema about the ankles. Fluoroscopy revealed a normal-sized left ventricle. Both auricles were markedly enlarged. Both inflow and outflow tracts of the right ventricle were enlarged. Marked dilatation of the pulmonary artery, affecting the trunk and both main branches, with calcification in the walls, was noted. Laboratory studies revealed a hemoglobin value of 14.3 grams with 6,260,000 red blood cells. The blood Kahn reaction was negative. Treatment consisted of bed rest, diurectis, and digitalis.

In June 1945 the patient was again hospitalized because of severe congestive failure, with a history of cold, cough, and sore throat for six weeks prior to admission. While in the hospital, she developed thrombophlebitis of the legs. Soon after, several episodes of acute chest pain followed by hemoptysis occurred and bilateral ligation of the femoral veins was performed. In November 1946 she was again hospitalized because of an exacerbation of congestive heart failure. In 1947 she was hospitalized on two occasions because of sudden chest pain, cough, and blood-streaked sputum, and a diagnosis of pulmonary emboli was entertained. Two other admissions in 1947, and three in 1948 were mainly for recurrent upper respiratory infections and exacerbation of heart failure. However, repeated pulmonary embolization may have played an important role du ing these episodes, which were marked by frequent attacks of sudden chest pain and hemoptysis.

Physical examination, made on admission in November 1948 following the automobile accident, revealed multiple bruises, cuts, and ecchymoses of the face, chest, and limbs. The patient was orthopneic and cyanosed. The point of maximum impulse was in the sixth intercostal space at the anterior axillary line. Findings on auscultation were similar to those heard on previous admissions. A phonocardiogram, recorded with the Sanborn Stetho-Cardiette, showed a systolic murmur after the first sound at the pulmonic and aortic areas. Systolic and mid-diastolic murmurs were recorded at the apex. The veins of the neck were distended. Moist râles were present at the lung bases. The liver was enlarged and tender, extending to 7 cm. below the right costal margin. The spleen was tender and palpable with deep inspiration. There was moderate ankle and sacral edema. The earliest available electrocardiogram, made in 1939 when she had pneumonia, showed a right-sided heart strain. A second electrocardiogram, made in February 1940 during convalescence from a severe episode of acute rheumatic fever, pancarditis, and congestive failure, showed the development of a block of the right bundle branch system. An electrocardiogram made during her last admission showed no significant changes from previous tracings. Fluoroscopic findings were similar to those of previous admissions.

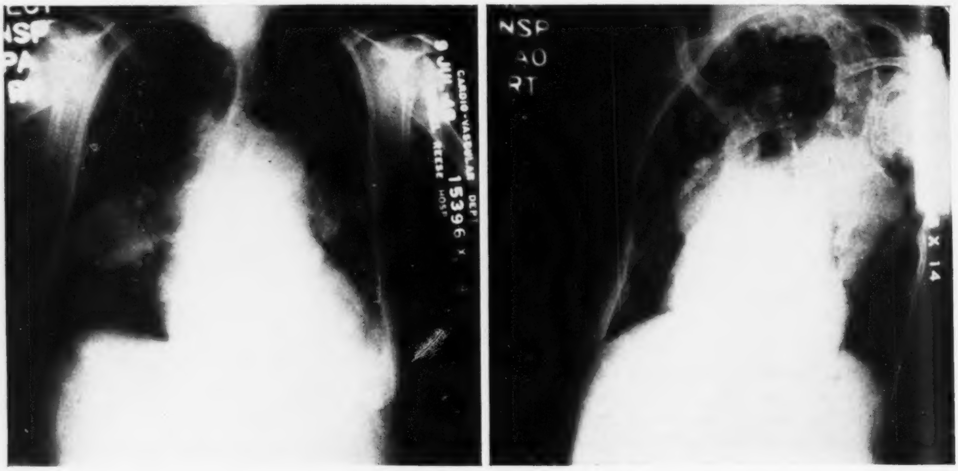

FIG. 1.—Teleoroentgenogram of the chest made in July 1948. Posteroanterior (*A*, Left) and left anterior oblique, (*B*, Right) views. (Discussed in text.)

A review of this patient's chest films revealed that marked aneurysmal dilatation of the pulmonary artery trunk and its two major branches was present as far back as 1933. The chest films exposed in 1940 showed a dense bilobular mass the size of a lime with incomplete calcification of the periphery in the right midlung field. The main trunk and left branch of the pulmonary artery were diffusely dilated. The radiologist who then had access to films taken in 1933 and 1936, noted that little change in the size of the lesions had occurred. In the earlier films, however, there had been no evidence of

calcification. Roentgenograms made during the patient's illness in 1943 showed an increase in size of the mass in the right midlung field, with less tendency to lobulation, and an increase in calcium deposit. No appreciable radiologic changes occurred in the next five years and roentgenograms made in 1948 (fig. 1) revealed no changes, showing chiefly three dense shadows within the chest, one in the right midlung field and two in the left side of the chest closer to the hilus.

This patient was seen by a number of different observers during her numerous admissions to the hospital. The most likely diagnosis considered was aneurysmal dilatation of the pulmonary artery and mitral stenosis. The possibility of an associated interauricular septal defect (Lutembacher's syndrome) was strongly entertained. The masses did not pulsate, however, and even with the aid of fluoroscopy, one could not rule out the possibility of lung cyst or tumor. The possibility of an A-V aneurysm was remote.

Physiologic Studies. It was decided that intracardiac catheterization would be of diagnostic help in this case, especially in determining the presence or absence of interauricular septal defect or other possible congenital shunt. The technic of right-sided heart catheterization as described by Cournand and colleagues[1] was closely followed. Blood samples were withdrawn in quick succession from the right and main pulmonary arteries, the right ventricle, right auricle, and superior vena cava. Roentgenograms were made and pressures recorded with a Hamilton manometer[8] at each position of the catheter. At the conclusion of catheterization, a sample of blood was withdrawn from the femoral artery. The oxygen content of the blood samples was determined by the method of van Slyke and Neill.[11] Blood-flow estimations were based on the principle outlined by Fick.[4] The patient's oxygen consumption was determined with a Sanborn Metabulator.

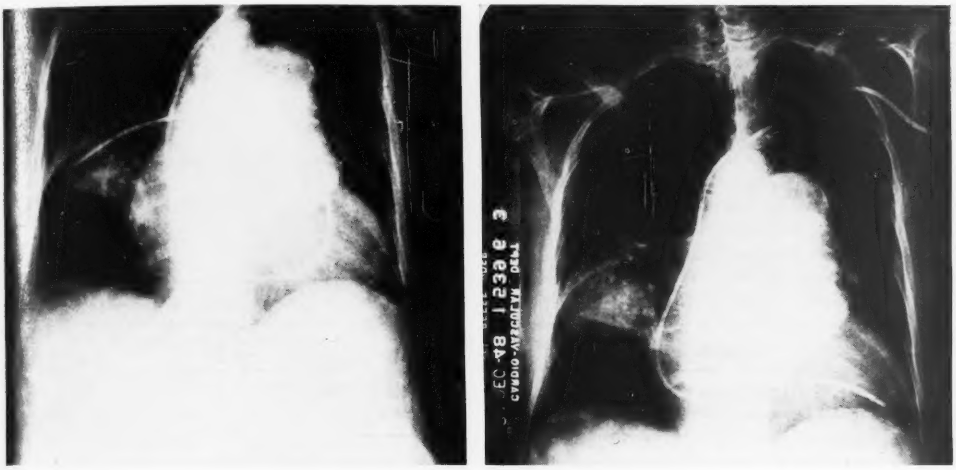

Fig. 2.—Anteroposterior films exposed with the patient in the supine position at a distance of four feet, by the Potter-Bucky technic. *A* (Left), The catheter has passed along the markedly dilated right pulmonary artery. *B* (Right), The tip of the catheter in the right ventricle demonstrates the tremendous size of that chamber.

Table 1.—*Summary of Data*

Catheter Location	Oxygen Vols. %	Systolic Pressure (Mm. Hg)	Diastolic Pressure (Mm. Hg)
Right pulm. art.	9.5	80	35
Main pulm. art.	10.9	80	35
Right ventricle	sample clotted	75	12
Right auricle	9.5	mean pressure =	
	10.6	+5	
Superior vena cava	10.1		
Femoral artery	12.9		

Resting oxygen consumption = 200 cc. per minute.

$$\text{Cardiac output} = \frac{200}{12.9 - 10.1} \times 100 = 6.9 \text{ liters}$$

per minute.

Results of catheterization are shown in table 1. The oxygen content of blood samples from the superior vena cava, the right auricle, and the pulmonary artery did not differ significantly. Pressures were definitely elevated in the pulmonary artery and right ventricle. The oxygen content of arterial

blood drawn from the femoral artery was 12.9 volumes per cent. The oxygen capacity was 19.4 volumes per cent and the arterial oxygen saturation was calculated to be 66.5 per cent. The patient's resting oxygen consumption was 200 c.c. per minute. By dividing the oxygen consumption per minute by the arteriovenous oxygen difference of the blood in the right auricle and the femoral artery the cardiac output was estimated to be 6.9 liters per minute. Figure 2, *A* shows the catheter in the markedly dilated right pulmonary artery and identifies it beyond doubt. In figure 2, *B* the tip of the catheter is in the right ventricle (as confirmed by pressure curves and blood oxygen content) and demonstrates the tremendous size of that chamber.

The catheterization studies led to the following conclusions: (1) Roentgenologic visualization of the catheter in the large masses established their identity as parts of a dilated pulmonary arterial tree. (2) Since the blood samples taken from the superior vena cava, the right auricle, and the pulmonary artery did not differ significantly in oxygen content, the possibility of the presence of a patent ductus arteriosus or of a septal defect was ruled out. (3) The marked unsaturation of the peripheral arterial blood strongly suggested the presence of pulmonary arteriolar disease with poor respiratory gas exchange. The relatively high cardiac output in all probability acted as a compensatory mechanism, similarly to what is noted in chronic cor pulmonale and in emphysema. (4) The high pressures in the pulmonary artery and right ventricle were likely due to a combination of (a) mechanical obstruction at the mitral valve, and (b) increased peripheral pulmonary resistance by an altered pulmonary arteriolar bed. The equality of systolic pressure in the pulmonary artery and right ventricle eliminated the possibility of pulmonary stenosis.

Comments

Clinical and physiologic studies would indicate that the main lesions present in this case were: (1) Marked aneurysmal dilatation of the main pulmonary artery and its major branches with calcification of the arterial walls. (2) Associated rheumatic heart disease with mitral stenosis. (3) An altered pulmonary arteriolar bed which may be primary, or secondary, to the mitral stenosis.

Greene and his co-workers[7] have recently reported 4 patients with idiopathic congenital dilatation of the pulmonary artery, apparently the first group of subjects in which physiologic studies were performed with the aid of intracardiac catheterization. They found normal pressures in the right ventricle and lower pressures in the pulmonary artery. They attributed the lower pulmonary arterial pressure to turbulence created by the deformity, to an increase in expansibility of the pulmonary arteries due to the thinness and dilatation of their walls, or to a relative stenosis caused by a stretching of the free edges of the semilunar cusps across the orifice of the valve. As mentioned above, in the patient here reported, the pressures obtained in the pulmonary artery are grossly elevated, therefore pointing to the presence of associated lesions.

The association of dilatation of the pulmonary artery and mitral stenosis has been described before. D'Aunoy and von Haam,[2] in their review of 85 patients with pulmonary aneurysms, noted 5 cases that were associated with mitral stenosis. In all 5, the pulmonary artery trunk alone was involved. In 4 of the 5 cases, sclerosis of the pulmonary artery, of unknown origin, was considered to be the main etiologic factor. The fifth case was one of congenital mitral stenosis, and a congenital defect in the pulmonary vasculature was believed responsible for the aneurysm.

Atheromatosis of the pulmonary arterial tree as well as pulmonary arteriolar sclerosis has been noted fairly frequently in association with dilatation of the pulmonary artery. Deterling and Clagett,[3] in a review of 36 cases of aneurysm of the pulmonary artery proved by necropsy, noted the presence of atheromas in 11 of the patients. In 3 out of these 11, there was marked arteriosclerosis throughout the lungs associated with right cardiac dilatation. They reported a patient of their own with aneurysmal dilatation of the right pulmonary artery, and severe sclerosis of the arterioles in both lung fields. Gibson[5] described a patient with a huge pulmonary artery, who after death was shown to have a primary proliferative arteriolar sclerosis of the pulmonary vessels. Gold[6] reported a case of congenital dilatation of the pulmonary artery trunk and the branches, associated with arteriosclerotic changes throughout the entire pulmonary arterial tree. On the other hand, Parker and Weiss,[10] in reporting on the structural changes in the lungs in mitral stenosis, described intimal proliferative changes in the larger

branches of the pulmonary arterial tree, marked fibrous thickening of the intima of the medium-sized arteries, and a hyperplastic arteriosclerosis of the arterioles.

On the basis of pathologic criteria set up by previous workers,[6, 7] one is not justified in regarding the present case as one of pure congenital dilatation of the pulmonary artery. On the other hand, it seems extremely unlikely that mitral stenosis, no matter how severe, even when giving rise to pulmonary arteriolar sclerosis and marked pulmonary hypertension, could, per se, lead to such massive diffuse dilatation of the pulmonary arteries. It is therefore believed that an inherent weakness, present in the arterial wall since birth, was a primary factor in allowing the dilatation to occur. Whether the pulmonary arteriolar changes which were suggested by this study were secondary to the mitral stenosis, or were congenital in origin remains unknown.

Summary

1. A case of marked diffuse dilatation of the pulmonary arterial tree associated with calcification in the walls has been presented.

2. The difficulties in determining the primary etiologic factors have been discussed.

3. The results of intracardiac catheterization have been described, and the conclusions reached have been discussed.

Acknowledgments

We are indebted to the other members of the Cardiovascular Department for their help in obtaining the data on this case and to Dr. L. N. Katz for his helpful suggestions in preparing this report.

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Sclerosis of the Chordae Tendineae of the Mitral Valve

By LEON SOKOLOFF, M.D., SAMUEL K. ELSTER, CAPTAIN, MC, AUS, AND NORMAN RIGHTHAND, M.D.

Thickening and sclerosis of the chordae tendineae of the mitral valve are seen fairly frequently in hearts that are not ordinarily considered to be rheumatic. In this report a systematic study of these lesions is presented. Factors involved in their pathogenesis and their significance in the development of the chronic rheumatic deformity are discussed.

IN NUMEROUS investigations concerning the sclerotic lesions of the valves of the heart, detailed descriptions of the rings and leaflets of the aortic and mitral valves have been made.[1–14] These various sclerotic changes have been interpreted as rheumatic, inflammatory, degenerative, or congenital. Although the chordae tendineae of the mitral valve are frequently thickened or otherwise deformed, they have apparently not been the object of systematic study. More than thirty years ago Felsenreich and von Wiesner[3] noted that a remarkably large number of isolated chordae were thickened or had low-grade fusion. The histologic appearance of such chordae suggested the extension of an inflammatory process from the leaflet. Previous writers had included these thickenings with the hyperplastic, noninflammatory changes of the mitral leaflet that take place with wear and tear. Deposition of lipid in the chordae, or at their insertions into the mitral leaflet, in persons beyond the third decade of life is common.[7, 9–11] Loss of cellularity and microscopic calcification occur at these sites as another manifestation of the aging of the connective tissue of the cardiac "skeleton."[10, 11] The likelihood that mechanical factors influence the development of these changes has been considered by several observers.[2, 11] Böhmig and Krückeberg[12] considered the sclerotic changes in the chordae and those of the insertional portion of the leaflet to be the result of various types of systemic infections, a response to foreign proteins "in the broadest sense."

In the present investigation the dimensions and histologic appearance of the chordae tendineae have been studied in human hearts that were considered grossly to be nonrheumatic. The extent and pattern of distribution of the sclerotic changes were thus determined and correlated with many factors of possible significance in the pathogenesis of the lesions.

METHODS AND MATERIAL

The study was made on 200 hearts examined at necropsy in Bellevue Hospital, New York. These included a large proportion from children, women, and Negroes. Many of the hearts from these were obtained through the courtesy of Drs. Milton Helpern, Robert Fisher, and Henry Weinberg of the Medical Examiner's Department of the City of New York. All hearts with distinct rheumatic lesions such as fusion of the chordae tendineae and all those from subjects with a history of rheumatic fever were excluded. The hearts were otherwise unselected.

The mitral valves were excised in the region of the annulus and at the origin of the chordae from the papillary muscles. They were fixed in a flattened position in 10 per cent formalin. Precise measurement of the diameter (width) of the chorda was made from photographic enlargements of both leaflets. The surfaces of the leaflets were wiped dry, the valve placed in the negative holder of a photographic en-

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larger (Federal #440), and the image projected onto photosensitive enlarging paper of medium contrast. The magnification used was three diameters. The leaflets were placed ventricular face down in the holder so that this surface was brought into prominence in the photographic image. It was decided that the length and width of the chordae inserting into the ventricular aspect of the leaflets (chordae of the second order [Tandler[15]]) were more amenable to measurement than were those of the chordae inserting into the free margin (chordae of the first order). Letters were used to designate the chordae on either side of the apex of the free margin of the anterior leaflet; the chordae on the anterior (left) side of this leaflet were labeled with a capital letter (A, B, C, and so on), while those on the posterior (right) side were marked with a lower-case letter (*a*, *b*, *c*, and so on). The width (diameter) was measured with calipers and was accurate to 0.1 millimeter. In the majority of instances the main trunk of the chordae was of fairly uniform diameter and offered no difficulty in measurement since major branching of the chordae took place shortly beyond the origin or close to the insertion. When major branching took place at a more intermediate position, the diameters of the branches rather than the main trunks were determined. The length of each chorda was measured between the origin and a line drawn on the photographs along the apex of the arcade between the insertions (fig. 1). Similar observations were made for comparative purposes on fifty bovine mitral valves.

Cross sections of the thickest chorda of the anterior leaflet were made for histologic study in each case. A strip of paper attached to the ventricular aspect with a 50 per cent solution of gum acacia was used to orient each specimen in the paraffin block. This permitted exact localization of sclerotic alterations. Sections were stained with hematoxylin and eosin, and, when the sclerosis was marked, with Weigert-van Gieson stains. The thickness of the central (fibrosa) layer and the external (subendocardial) layer was measured with an eyepiece micrometer. Sections of the mitral leaflet were made when the chordae were sclerotic. Sections of myocardium were available except from the hearts of 15 infants or young individuals and 5 adults obtained from the medical examiner's office. In none of these 20 hearts was there appreciable sclerosis.

The following data were recorded when available: weight of the heart; age, sex, race, and arterial blood pressure of the subject; an estimate of the degree of generalized arteriosclerosis; circumference of the ring of the mitral valve; the presence of calcification in the annulus of the aortic and mitral valves, myocardial infarction, pericarditis, and syphilitic aortitis.

The width of a chorda tendinea approximates its diameter only when the chorda is almost round on cross section. In 13 of the adults and 7 of the infants and children, the widest chordae were markedly flattened and measurements of these chordae have been excluded from the calculations.

Results

Casual inspection of the valves revealed a relative thickening of certain chordae tendineae of the anterior leaflet of the mitral valve in every heart. The histologic sections of the thickest chorda disclosed that most of its substance was made up of relatively acellular collagen. This material was usually directed, in a normal fashion, parallel to the long axis of the chorda. In the hearts from subjects in the third decade of life or older, a subendocardial layer of collagen frequently encircled this central core, at least in part. When this circular layer was thick, it constituted the bulk of the cross section and could even be distinguished grossly. Such enlarged and altered chordae were readily identified as abnormal (fig. 2). Obviously, there has been an accretion of tissue. A certain degree of subendocardial thickening can be interpreted as analogous to the stratification that occurs in the leaflets of the mitral valve with aging.[10] Chordae that showed only slight subendocardial thickening without gross enlargement were classified as *normal* for the adult. Those with a thick subendocardial ring were listed as *sclerotic* chordae tendineae. Separate categories were made for *infants*, 1 year of age or less, and *children*, below 16 years. As stated

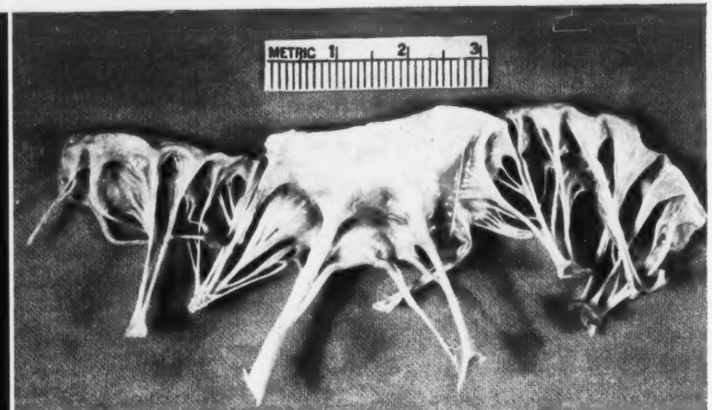

Fig. 1.—(Left) A working-type photograph of the ventricular aspect of the mitral valve; anterior leaflet above and posterior leaflet below. This is one of the normal adult specimens. Because this is a negative image, the relative positions of the lettered series are inverted; that is, in the actual specimen, chordae designated with capital letters appear on the right and those with lower-case letters on the left. (×1/3.)

Fig. 2.—(Upper right) Mitral valve with sclerotic A and *a* chordae tendineae of the anterior leaflet. From an 82 year old white man. The *a* chorda is 2.2 mm. wide and 26.7 mm. long. The average diameter of the chordae of the posterior leaflet is 0.32 mm. while the average length is 21.3 mm.

Fig. 3.—(Lower right) Mitral valve with mild rheumatic deformity. There is gross sclerosis of the second order chordae of the anterior leaflet and the adjacent right posterior leaflet chordae. The remaining posterior leaflet chordae are delicate.

TABLE 1.—*Diameters of Thickest Second Order Chorda Tendinea of Anterior Leaflet (in millimeters)*

	Normal (Adult)	Infants	Children	Sclerotic (Adult)
Average	0.86	0.37	0.50	2.15
Range	0.4–1.5	0.2–0.5	0.4–0.7	1.2–3.8
Standard deviation	±0.20	—	—	—
Number of cases	149*	10 (7)†	17 (13)†	11

* Thirteen cases in which the widest chorda tendinea was flattened are not included in this table.

† The figures in the parentheses represent the number of hearts with chordae that were not flattened and were therefore suitable for the above calculations. The figures not in parentheses include both types of chordae.

those of the posterior. The diameter of the thickest of these followed a normal-type distribution curve (fig. 4). The scatter of variation between the posterior leaflet chordae is

TABLE 2.—*Average Diameters of Second Order Chordae Tendineae of Posterior Leaflet (in Millimeters)*

	Normal Chordae (Adult)	Sclerotic Chordae (Adult)
Average	0.35	0.35
Range	0.19–0.56	0.29–0.42
Standard deviation	±0.07	—
Number of cases	149	11

TABLE 3.—*Lengths of Second Order Chordae Tendineae (in Millimeters)*

	Average Posterior Leaflet	Anterior Leaflet						Ratio: Length of Thickest Anterior to Average Posterior
		C	B	A	a	b	c	
Average of normal chordae (adult)	18.0	18.0	19.0	19.0	21.5	21.6	19.1	1.14
Range	10.1–29.0	9.0–33.3	10.0–28.7	7.3–32.3	9.3–43.3	9.3–35.0	9.0–38.3	0.66–1.72
Standard deviation	±3.3	—	—	—	—	—	—	±0.22
Number of cases	149	134	147	149	148	149	139	149
Average of sclerotic chordae (adult)	17.3	16.7	17.5	19.7	20.9	20.1	20.5	1.18
Range	12.2–22.4	12.3–21.0	11.7–24.0	13.0–26.0	14.3–26.7	15.0–26.3	15.0–23.7	0.88–1.56
Number of cases	11	10	11	11	11	11	6	11

previously, measurements were not made on *flattened* (adult) chordae. The distribution of cases in each category was as follows:

Infants: 10 cases	
Normal chordae	7
Flattened chordae	3
Children: 17 cases	
Normal chordae	13
Flattened chordae	4
Adults: 173 cases	
Normal chordae	149
Flattened chordae	13
Sclerotic chordae	11
Total	200

Dimensions of the Chordae Tendineae (Tables 1–3). In the normal group, there was in every heart a relative thickening of certain of the chordae of the anterior leaflet compared with

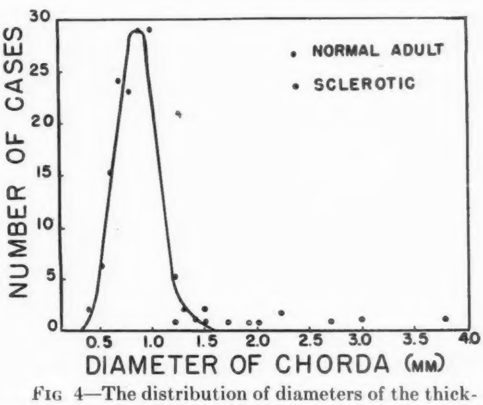

FIG. 4—The distribution of diameters of the thickest chordae tendineae of the anterior mitral leaflet in adults.

much smaller. The relative thickening of an anterior leaflet chorda may be expressed as the

ratio of its diameter to the average of the diameters of the posterior leaflet chordae. In the *normal* group this average value was 2.5. In most instances the thickest chordae were those most central of the anterior leaflet (A, B, *a*). This relationship obtained also in *infants* and *children*. In 50 bovine hearts the average diameter of the thickest chorda tendinea of the anterior leaflet was 1.6 ± 0.04 mm. and the general average of the individual average diameters of the posterior leaflet chordae tendineae was 0.7 ± 0.03 mm., a ratio of 2.3.

In the 11 *sclerotic* hearts the diameter of the chordae was in general very greatly increased. Usually only one or two of the chordae were involved and in this group also the site of predilection for the thickening was the *a*, A, or B position. In addition, in the group with *flattened* chordae, thickening due to similar histologic alteration was found in two isolated posterior leaflet chordae and in one anterior leaflet chorda; these are excluded from the present calculations.

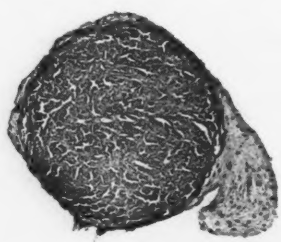

FIG. 5.—Cross section of the thickest second order chorda tendinea of the anterior mitral leaflet of a 6-month-old infant. Nuclei of fibroblasts are discernible in the central core, and their main axis in some instances is in the plane of the section. (Hematoxylin and eosin stain. ×80.)

In the *sclerotic* group the thickening did not involve the chordae of the posterior leaflet; the average diameters of the latter were the same in the *sclerotic* and *normal* hearts.

In most instances the sclerosis involved the entire length of the chorda. Occasionally there was fusiform swelling of only the trunk of the chorda or a tapered thickening at the insertion into the leaflet.

The lengths of the chordae tendineae of the anterior leaflet varied greatly, usually to a much greater degree than did those of the posterior leaflet. Their relative length in each heart has been expressed as a ratio of the length of the anterior leaflet chorda to the average of the lengths of the chordae of the posterior leaflet. In general, the second order chordae of the anterior leaflet were only slightly longer (1.14) than those of the posterior leaflet. In the sclerotic anterior leaflet chordae the relative length was 1.18. This difference is insignificant and demonstrates that the process of sclerosis was not accompanied by shortening.

Histologic Structure. The collagenous core of the *normal* chorda was continuous with the dense fibrosa layer of the leaflet. In infancy and early adult life it was largely acellular, but the collagen was clearly fibrillar. At this time the fibrils were wavy and therefore coursed for a distance in the plane of the cross section although mostly they were directed in the plane of the axis of the chorda (fig. 5). With aging the collagen became less fibrillar, and formed more compact, less cellular bundles. The subendocardial circular layer was rarely prominent in subjects younger than 30 years of age. When it first became prominent it was loosely arranged, and paler than the central core and more cellular. In older subjects in the later decades of life it, too, became hyalinized although the circular arrangement clearly persisted.

In the flattened chorda the collagen was arranged either as a single flattened dense band or as two partially fused, round bundles contained within a single endocardial sheath (fig. 6). The former pattern was more frequent than the latter. The main trunk of a chorda typically had a single core before it gave off its branches.

The *sclerotic* chordae were composed principally of hyalinized collagen arranged in concentric circles. In the mildest form, this circular layer surrounded a moderately well-preserved central core of axially arranged fibers, while in more advanced lesions the central core became atrophic (fig. 7). In several cases, two or three such axial bundles were found. With Weigert-van Gieson stains, frayed elastic tissue fibrils were seen at the periphery of these axial bun-

dles. The subendocardial layer was stippled with calcific granules in one specimen. The leaflet was thickened also at the insertion of the chorda; when the chorda was sclerotic, this thickening was produced by hyaline collagen and irregular areas of looser, pale, basophilic fibrous tissue. In only two instances was there considerable thickening of the remainder of the leaflet as well. In only one example did the

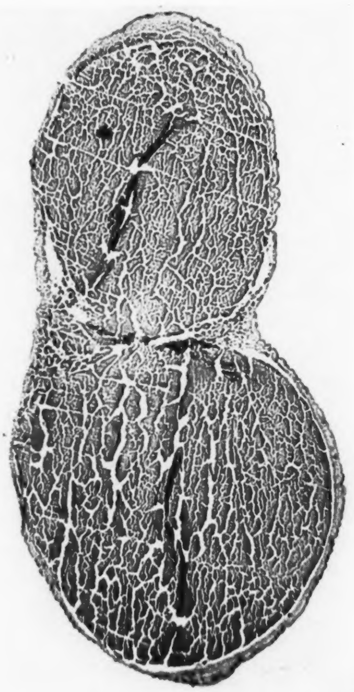

FIG. 6.—Cross section of a flattened chorda tendinea of anterior mitral leaflet of a 72 year old white man. In this instance there are two distinct central cores incompletely separated by the partition of the subendocardial layer. Note the absence of cells. (Hematoxylin and eosin stain. ×80.)

leaflet or valve ring contain blood vessels; these were of the thick-walled type seen commonly in hearts with healed rheumatic valvulitis. The sections of myocardium revealed no Aschoff bodies or paravascular scars. Frozen sections of several of the sclerotic chordae stained with sudan 4 revealed very little lipid. Except for fibroblasts and a few mononuclear cells, there was no cellular reaction. The original core of the chorda was usually centrally placed in the area of thickening.

Influence of Age, Race, and Sex. Sclerotic chordae were found only in the hearts of white men from 37 to 82 years of age. If flattened chordae are excluded, there were no sclerotic

FIG. 7—Section of a sclerotic anterior leaflet chorda from a 62 year old white man. The circular subendocardial layer is greatly increased in thickness and there is atrophy of the central core. (Weigert-van Gieson stains. ×35.)

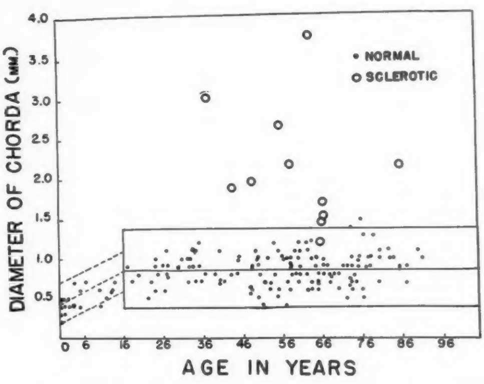

FIG. 8.—The relation between the diameter of the thickest chorda tendinea of the anterior leaflet and the age of the subject.

ones in 65 individuals less than 35 years of age. No progressive increase of incidence with age was noted among the hearts of the 11 subjects with sclerotic chordae who were older than 37 years of age (fig. 8). Nevertheless, age would appear to be an important factor in the pathogenesis of this lesion since it was not found in

subjects who had not reached the fourth decade of life.

There were 122 white and 38 Negro adults in the series. Nine per cent of the former and none of the latter had sclerotic chordae. At first glance this would seem to be a significant difference. Yet Negroes constituted 69 per cent of the adults below 36 years of age and only 12 per cent of those above, and the absence of sclerosis in this group may be due to the younger age. It cannot be denied, however, that the reverse may be true, namely, that the absence of sclerosis in the younger group may theoretically be attributable to the high proportion of Negroes.

There were 112 adult males and 49 females. Nine and eight-tenths per cent of the men but none of the women had sclerotic chordae. Fifty-nine per cent of the young adults were women, whereas in the older group the women comprised only 25 per cent. The sex difference may therefore be attributed in part to age factors. The series is too small to allow a definitive statement in this regard. We have noted sclerotic chordae tendineae in the heart of a woman not included in this series.

Influence of Blood Pressure, Weight of Heart, Arteriosclerosis, and Other Lesions. Blood pressure readings were available in 116 of the 160 adults; 106 had normal chordae while in 10 there were sclerotic chordae. The subjects whose blood pressure readings were available were grouped into three classes: those with low blood pressure (less than 100/70)—4; those with normal blood pressure (100/70 to 148/88)—75; those with high blood pressure (150/90 and higher)—37. The incidence of the thickening of chordae of the normal type was almost identical in the hypertensive and normotensive groups. Two of the 10 patients with sclerotic lesions (20 per cent) had hypertension; 34 per cent of the persons with nonsclerotic chordae had elevated blood pressures. Arterial hypertension was thus not a significant factor in the development of this lesion.

The weight of the heart in the adults bore no relation to the diameter of the thickest chorda tendinea of the anterior leaflet or to the development of the sclerosis (fig. 9). The latter was seen in hearts weighing from 170 to 620 grams. The heart weighed more than 400 grams in only 2 subjects with sclerotic chordae. In general the length of the chordae of the second order was greater in hypertrophied hearts than in small ones, but there was much individual variation. The circumference of the mitral ring could not be correlated with the presence of the lesion.

The degree of generalized arteriosclerosis was graded as none, mild, moderate, or severe. There were 17 young adults without appreciable arteriosclerosis. Sclerosis of the chordae tendineae was not present in any of these nor in the other young adults who had some arteriosclerosis. Among the older group 7.6 per cent of those with mild, 5.6 per cent of those with moderate, and 10.8 per cent of those with severe arteriosclerosis had marked lesions of the chordae. Similarly there was no striking correlation with the incidence of myocardial infarction or calcification of the rings of the mitral or aortic valves.

In 2 of the 11 subjects with *sclerosis* there was an associated syphilitic aortitis without insufficiency of the aortic valve. Pericarditis was absent in all eleven. In 2 subjects the principal anatomic diagnosis was pulmonary tuberculosis; in four there was a carcinoma of the upper gastrointestinal tract; in the remaining the diagnoses included generalized arteriosclerosis, and duodenal ulcer with perforation.

Discussion

The results demonstrate that relative thickening of some of the chordae tendineae of the second order of the anterior mitral leaflet occurs with regularity in the human heart. Two types may be distinguished: (1) thickening as a normal structural pattern, or (2) an acquired sclerotic thickening.

That the first type of thickening of the chordae in this region is inherent in the construction of the valve is indicated by the regularity of its occurrence in human beings of all ages, even in newborn infants, and in animals (e.g., bovine) in which acquired rheumatic or arteriosclerotic heart disease is not known to occur. It usually is of mild degree but the diameter of these chordae may be two to three times or

more than that of the chordae of the posterior leaflet. In most instances the entire chorda is thickened. Little is known of the fetal development of the chordae tendineae. Cordier and Roux[16] have described them in several early embryos. In a 9.5-mm. embryo the anlage of second order chordae may be seen on the anterior ("internal") leaflet. In the 13.5-mm. embryo, as the bulbus arteriosus divides and the interventricular septum is completed, the chordae of the anterior leaflet undergo resorption. This leaves a chorda-free hiatus and the thickened chordae are on either side of this gap. This position would suggest that mechanical factors, stemming from the character of the blood flow in this region, influence the thickness of these chordae. As aging takes place, the collagen of the chorda becomes more compact and hyaline. Feitelberg and Kaunitz[17] in x-ray diffraction studies of the chordae tendineae of the human heart noted increasing orientation of the collagen molecules in the axis of the chordae after childhood. The histologic appearance of the central core of collagen suggests an axial arrangement of the fibrils. In infancy and childhood these fibrils are wavy and run, in part, therefore, in the plane of the cross section as well.

The pathogenesis of the *sclerotic* type of thickening is difficult to evaluate. Its location suggests that mechanical factors may be concerned. As in the normal group, the central chordae of the anterior leaflet are chiefly involved. This suggests that the same factors may be involved in both varieties of thickening. Sclerotic changes in other parts of the cardiovascular system have been attributed to mechanical influence such as the local blood pressure and the fixation or mobility of the part. It is noteworthy that the region of in-

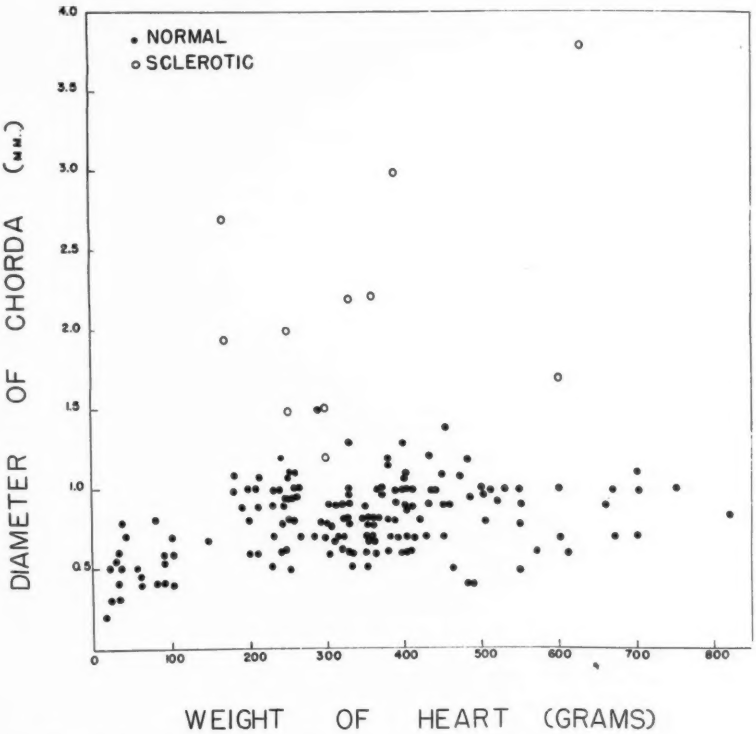

FIG. 9.—The relation of the diameter of the thickest chorda tendinea of the anterior leaflet to the weight of the heart.

sertion of these central chordae into the ventricular aspect of the anterior leaflet of the mitral valve unlike the region of insertion in the posterior leaflet is very frequently the site of atheromatous deposits. Such plaques may be seen to extend to the contiguous portions of the chordae. This does not imply necessarily that this chordal sclerosis is simply a process of atherosclerosis. Indeed there is no simple correlation between the degree of atherosclerosis of

FIG. 10.—Section of chorda tendinea from the rheumatic mitral valve shown in figure 3. The central core is markedly atrophied and the thickening is caused by the presence of a broad layer of circularly arranged collagen fibers. (Weigert-van Gieson stains. ×30.)

the leaflet and the sclerosis of the chorda. The importance of the mechanical factor is suggested by the observations that the sclerosis sometimes occurs with the sclerosis of the anterior mitral leaflet that accompanies insufficiency of the aortic valve due to syphilis or to isolated calcific stenosis of the aortic valve.

The fact that the chorda may be more sclerotic than the leaflet, and that the sclerosis may even be focal at a distance from the leaflet, contradicts the thesis that these changes are simply due to extension of an inflammatory (or other) process from the leaflet on to the chorda.[12]

On the other hand, there are certain features of close similarity of this lesion to those of healed rheumatic valvulitis. The pattern of subendocardial fibrosis may be indistinguishable in the two. The existence of several axial bundles of collagen within the thickened mass may correspond to the fusion of the chordae.[18] The striking similarity between the thickened chordae of healed rheumatic inflammation and the sclerotic chordae of the present series may be noted in figures 7 and 10. It cannot, however, be assumed that the existence of more than one axial bundle within the sclerotic chorda necessarily proves that fusion of pre-existent chordae has taken place and that the lesion is, therefore, of rheumatic origin. There may be, as pointed out previously (fig. 6), more than one fibrous core initially within a normal chorda tendinea. Furthermore, a single central core may conceivably become disorganized into two or more bundles during the process of sclerosis. One may speculate that the laying down of collagen in the present instance compensates for the weakening of the central core that attends its atrophy. It may be pointed out that the atrophy of this structure in the rheumatic cases is more likely secondary to the fibrosis, associated with the healing of endocardial and subendocardial inflammation. May not the attenuation of the central core be the result of the sclerosis in the present series as well? Other facts that argue against the rheumatic origin in these cases are the absence of fusion and shortening of the chordae, vascularization of the ring and leaflet (except in one instance), characteristic myocardial scars, pericardial adhesions, history of rheumatic fever, and the failure to find such sclerosis in younger adults. Furthermore, milder degrees of subendocardial sclerosis are seen in a large proportion of the normal adult hearts.

The similarity of the appearance of the *sclerotic* chordae to those of the healed rheumatic lesion suggests another possibility. In the milder examples of healed rheumatic valvulitis, in which the landmarks are not entirely destroyed, the earliest and most severe damage involves the chordae of the anterior leaflet,

particularly in the region of the right posterior wall attachments (the *a*, *b*, *c*, *d* positions according to the present scheme of nomenclature) (fig. 3). The previously mentioned considerations would suggest that mechanical factors may possibly accentuate the development of the fibrosis in chronic rheumatic deformity of the chordae of the valve also. Such a concept is consistent with the commonplace observations that fibrosis and stenosis far more frequently complicate acute rheumatic inflammation of the mitral than of the tricuspid valve.

That repeated systemic infections, or other toxic states in which foreign proteins may be present, may play a role cannot be disproved. Nevertheless severe chronic inflammatory foci were not found more frequently in individuals who had marked sclerosis of their chordae than in those who did not.

Summary

The dimensions and histologic appearance of the second order chordae tendineae of the mitral valve were studied in 200 human hearts that were considered grossly to be free from rheumatic inflammation. Two types of relatively thick chordae were found. The central chordae of the anterior leaflet were thickened in all hearts, in subjects of all ages, and a similar pattern was found in the bovine heart. This suggests that this finding is a normal developmental phenomenon. Another type of thickening was seen in 11 of 160 adult hearts. This was of much greater extent and was associated with laying down of large amounts of subendocardial collagen. Of the many factors possibly involved in the pathogenesis of this sclerosis, only two are suggested to be of importance: (1) the lesion was not seen in subjects younger than 37 years of age, and age, therefore, plays a role; (2) the predilection of central chordae of the anterior leaflet of the mitral to undergo this change suggests that mechanical factors, stemming from the character of the blood flow in this region, also are involved.

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Healed Dissecting Aneurysm of the Aorta Erroneously Diagnosed Paramediastinal Effusion; Death Following Attempted Aspiration

By J. Chandler Smith, M.D., and Salvatore M. Sancetta, M.D.

Approximately 1 per cent of dissecting aneurysms of the aorta develop re-entry tears and heal, forming the so-called "double-barrelled" aorta which is compatible with a variable period of survival. Occasionally a case is found wherein the dissection has remained limited to the media, healing without evidence of intimal tears. We describe such a case, so rare as to constitute a medical curiosity.

Two unusual features have prompted us to report the following case of dissecting aneurysm of the aorta. The x-ray shadow of the aneurysm was interpreted as due to a paramediastinal effusion in a patient with known pulmonary tuberculosis. An attempted aspiration led to perforation through the dissection into the lumen of the aorta which resulted in a fatal cardiac tamponade. At necropsy the aorta exhibited a healed medial dissection with complete absence of an intimal tear.

Case Report

W. F., a 27 year old white man, was known to have had pulmonary tuberculosis since 1938. The pulmonary lesions had been progressive despite intermittent bed rest. A right pneumothorax was performed in 1943 and a left pneumothorax in 1946. The last examination prior to the onset of the present illness was made on Feb. 25, 1948, following return to work. A complete physical examination at this time revealed no cardiac murmurs and a roentgenogram of the chest (fig. 1, *A*) disclosed bilateral pulmonary tuberculosis, a mediastinum of normal width, and no cardiac enlargement. Bilateral intrapleural pneumothoraces were maintained.

On April 27, 1948, the patient noted the onset of intermittent substernal pain without radiation and not related to exertion. On May 7, 1948, as he stepped down from a streetcar, he suddenly became short of breath and developed severe substernal pain radiating into the neck and the left arm. The pain persisted for twenty-four hours and then gradually subsided during the next four days. The shortness of breath was constant and moderately severe. X-ray examination of the chest on May 18, 1948 (fig. 1, *B*) revealed a convex bulge of the right border of the mediastinum at the level of the hilus of the right lung. This was thought to represent a loculated pleural effusion and the patient was permitted to continue in his employment as a piano player. However, because of constant shortness of breath, epigastric pain, and anorexia of four days' duration, he was readmitted to the hospital on June 12, 1948. On the day before admission there was one episode of expulsion of dark brownish-red vomitus.

The temperature was 37.5 C., the pulse rate 110, the respiratory rate 30, and the blood pressure 170/70. Physical examination revealed a poorly nourished and chronically ill white man who was slightly cyanotic. There was a moderate funnel-shaped deformity of the chest. Bronchial breathing and increased dullness to percussion were noted over the apices of both lungs. Coarse râles were audible over the posterior base of the right lung. The heart was not clinically enlarged. A blowing, high-pitched diastolic murmur was heard over the third left parasternal area, transmitted well to the aortic auscultatory area. A blowing systolic murmur was heard best at the base and transmitted faintly to the apex. The second aortic sound was barely audible. The edge of the liver was barely palpable and slightly tender. There was no edema of the extremities or enlargement of lymph nodes. The reflexes were normal.

The hemogram revealed 10 grams of hemoglobin, and 3,500,000 erythrocytes per cu. mm. of blood. The urine was normal. The reaction to the Kline test for syphilis was negative. An x-ray examination of the chest revealed findings similar to those shown in the previous film. In addition there were an apical pneumothorax on the right, a small pleural

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effusion at the right base, and scattered mottling throughout both lungs with several foci of calcification within the right and left upper lobes.

The clinical diagnoses were: loculated pleural effusion at the hilus of the right lung and bilateral pulmonary tuberculosis. On the second hospital day, aspiration of the pleural effusion was attempted. An 18-gage needle was inserted into the right second intercostal space 2 cm. from the border of the sternum and directed in an inferior and medial direction. At a depth of approximately 6 cm. the syringe suddenly filled with arterial blood and the needle was withdrawn. Shortly afterward the patient became pale, apprehensive, and severely dyspneic. The blood pressure was unobtainable and death occurred ten minutes after the aspiration.

Gross Postmortem Findings. The pericardial sac was distended with approximately 800 cc. of bloody fluid and blood clots. A needle puncture tract over the anterior surface of the pericardium opened into a sac of the aortic wall. This sac formed at the level of the sinuses of Valsalva, beneath the superior reflection of the pericardium, and extended for a distance of 6 cm. along the ascending aorta. The sac measured 2 cm. in depth and extended around all but 2 cm. of the circumference of the base of the aorta. There was slight compression of the base of the pulmonary artery (fig. 2). The lower part of the external wall of the sac was covered on its outer surface by blood-stained epicardium and the upper portion by adventitia and fibrous tissue of the mediastinum. The sac was filled with blood, and when evacuated, presented a pale, yellowish-gray,

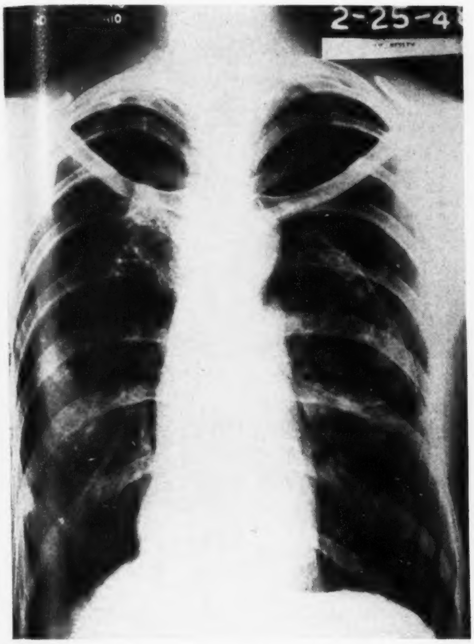

FIG. 1.—*A*, Posteroanterior view of the chest taken February 25, 1948. The mediastinum is of normal width. The heart is elongated and midline in position, and there is slight prominence of the pulmonary conus. There are bilateral pneumothoraces and diffuse pulmonary infiltration.

FIG. 1.—*B*, Posteroanterior view of the chest taken on May 18, 1948, following the episode of acute substernal pain. The mediastinum is now considerably widened. There is a pleural effusion at the right base.

finely irregular lining surface. The internal wall of the sac was composed of a thin lamina of aortic wall. The position of the puncture holes of the sac indicated that a needle had entered the pericardial sac, pierced the external sac wall, traversed this sac, and then punctured the internal wall to enter the lumen of the aorta. Gross examination of the remainder of the aorta was not remarkable except for scattered yellowish-gray intimal plaques particularly about the ostia of the intercostal vessels and between the renal arteries and iliac bifurcation. There was no evidence of a healed intimal tear.

The heart weighed 480 grams. The right and left ventricles measured 0.6 and 1.6 cm. in thickness respectively. The circumferences of the heart valve

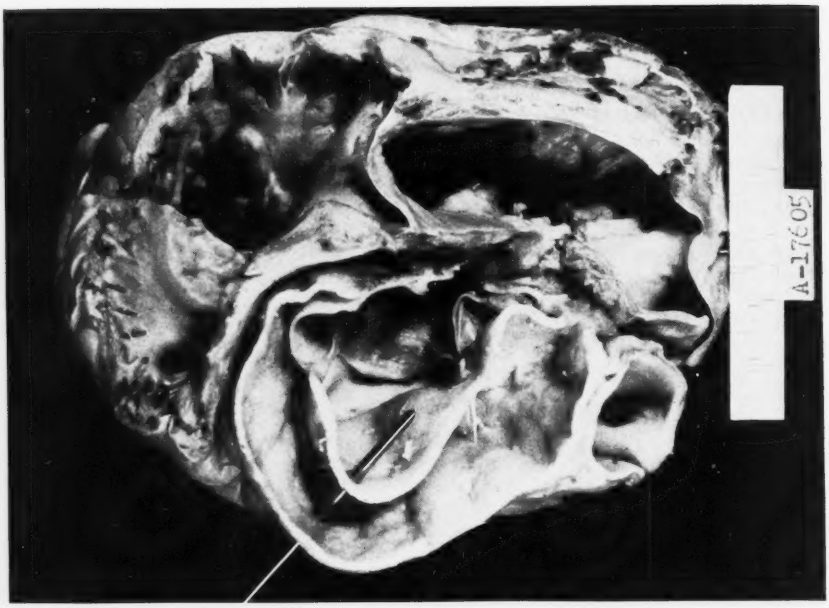

FIG. 2.—The base of the heart showing the great vessels and the intramural sac of the aorta.

rings were within normal limits. The leaflets of the mitral valve were slightly thickened and somewhat nodular along the line of closure. There was slight fusion of the commissures of the aortic cusps. None of these valvular changes appeared to be functionally deforming.

The right and left lungs weighed 600 and 700 grams respectively. The bases were adherent to the thoracic wall by fibrous adhesions and the apices were smooth except for a single fibrous band attaching the right apex to the overlying cupola. Approximately 200 cc. of clear pale-yellow fluid were present in each pleural cavity.

There was recent erosion of the mucosa of the esophogus and severe chronic passive hyperemia of the gastric mucosa and of the liver. The ileum revealed two approximately round ulcers of the mucosa with thickened borders and dark reddish-gray granular bases. Similar mucosal ulcers were found in the colon. The remaining findings of the autopsy were not remarkable.

Microscopic Postmortem Findings. The sac had been formed by a separation of the media of the aorta so that the outer wall was composed of loose, young fibrous tissue containing a thin layer of elastic fibrils. The inner wall of the sac was composed of aortic media lined on one surface by intima and on the sac surface by young fibrous tissue covered by endothelium. The elastic fibrils of the inner wall of the sac composing the media of the aorta were irregularly disposed and revealed minute foci of necrosis. The lining surface of the sac was covered by endothelium beneath which were a few phagocytes containing brown pigment granules that were positive for iron stain. Several small, similar sacs, occasionally filled with blood, were present within the aortic media just proximal to the large sac. Microscopic sections from the thoracic and abdominal aorta revealed no changes other than those of moderate arteriosclerosis.

Microscopic examination of the lungs revealed fibrocaseous tuberculosis, focal pulmonary fibrosis, and chronic pulmonary emphysema. The esophogeal ulcers were nonspecific and those in the ileum and colon were tuberculous.

The pathologic diagnosis was dissecting aneurysm of the aorta with intramural aortic sac. There had been perforation of this sac by a needle with hemopericardium and cardiac tamponade. Other pertinent diagnoses included hypertrophy and dilatation of the heart, nondeforming endocarditis of the mitral and aortic valves, fibrocaseous pulmonary tuberculosis, ulcerative tuberculous entero-colitis, and acute and chronic esophagitis.

Discussion

The differential diagnosis of dissecting aneurysm of the aorta has been discussed in numerous publications and does not merit mention here. A review of 698 cases of dissecting aneurysm of the aorta by one of us in a previous report[8] disclosed no similar instance of aortic dissection that was clinically mistaken for a paramediastinal effusion. In retrospect the history was fairly typical, and the appearance of a well-defined aortic diastolic murmur only a few months after the patient's heart had been found normal should have made one suspicious of the correct diagnosis. There was no evidence pointing to a recent inflammatory lesion of the aortic valve.

Healed dissecting aneurysm of the aorta has been clinically mistaken for tumor of the mediastinum. In the case reported by Patrick and Taylor[7] the patient, a 32 year old white man, underwent an exploratory laparatomy two years after the onset of intermittent epigastric and low left-sided chest pain, a history suggesting gastric ulcer, which was not found at operation. He later developed progressive dysphagia and chest roentgenograms showed a large, nonpulsating mass which displaced the esophogus forward and to the left. Thoracotomy was undertaken and upon incision of the mass marked hemorrhage occurred. Death occurred one week later, and necropsy revealed a large dissection filled with laminated clot extending from the arch of the aorta to 4 cm. below the diaphragm where a small re-entry foramen was found. At the proximal end of the dissection there was a transverse scar of the intima that was thought to be a healed intimal tear.

Von Möllar[9] described the first case to be reported of dissection of the aorta in the absence of rupture and of intimal tear. In Krukenberg's patient, reported in 1920,[5] the main aortic dissection communicated with the lumen of the aorta, but in both inferior thyroid arteries there were numerous raised cystlike nodules, within the media, filled with blood and very similar to the smaller lesions found in contiguity with the main dissection in our patient. The third such case reported was that of Whitman and Stein[10] in 1924, as an incidental finding at necropsy. There was a healed, endothelialized dissection of the aorta extending from the root of the aorta to within 10 cm. of the iliac bifurcation. The sac surrounded the

aorta in its entirety with the exception of the posterior portion overlying the vertebral bodies and was filled with a clear, lymphlike fluid. There was no evidence of an intimal tear and the sac had evidently never communicated with the lumen of the aorta.

These cases support the tenet first propounded by Babes and Mironescu,[1] and later clarified by Erdheim,[2] that medial disease precedes the intimal tear, with secondary rupture of the intima and forceful extension of the dissection by the column of blood. In our patient the contents of the sac during life could not be ascertained because of the unique perforation, but there was certainly no evidence of antemortem clot. Here, too, the sac may have contained a transudate.

The clear-cut appearance of a classical aortic diastolic murmur likewise supports the now generally accepted thought that such a murmur is due to insufficiency created at the aortic orifice by distortion caused by the bulging dissection, as opposed to the views of Letulle[6] and of Keefer and Resnik[4] who held that the diastolic murmur arose in the eddies produced at the lip of the intimal tear by the inflow and outflow of blood.

In our patient there were signs of early congestive failure which most likely would have caused death at a later date. Gouley[3] has shown that when healed dissecting aneurysm produces aortic insufficiency, death occurs in congestive failure indistinguishable from that due to intrinsic lesions of the aortic valve.

Summary

A case of chronic healed dissecting aneurysm of the aorta is presented in which the dissection was limited to the media; there was no intimal tear, no rupture, and no area of reentry. The dissection was mistaken for a paramediastinal effusion, and death was due to cardiac tamponade incident to exploratory needle aspiration. At necropsy the needle was found to have penetrated the superior pericardial reflection, the outer sac wall, the sac cavity, and the lumen of the aorta.

Acknowledgment

We are indebted to Dr. Harold Curtis, Director, Sunny Acres Tuberculosis Sanatorium, Warrensville, Ohio, for furnishing us with the clinical data and for permission to report this case.

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Primary Myosarcoma of the Heart

Report of a Case Associated with Malignant Carcinoids and Pancreatic Heterotopia

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Precordial pain and pericarditis were the early manifestations of this cardiac tumor. Discovery of bony metastases preceded detection of a rapidly growing intrathoracic mass, erroneously considered a bronchiogenic carcinoma invading the heart. Changing murmurs, chest pain, transient arrhythmia, intermittent fever, and progressive weight loss were the outstanding clinical features. Necroscopy revealed a primary cardiac tumor with metastases to pelvic bones, vertebrae, and lung, as well as malignant carcinoids and heterotopic pancreatic tissue.

PRIMARY malignant muscle tumors of the heart are uncommon enough to warrant reporting a single case. The tumor in our case we have classified as a myosarcoma, as it is closely related to the malignant striated muscle tumors of the heart but less differentiated. Only eight striated muscle sarcomas primary in the heart have been described. Leach,[12] reporting such a case, found in the literature 422 primary tumors of the heart and pericardium, of which 89 were sarcomas of different types. Whether the tumor in our case arose from the heart or pericardium could not be determined with certainty, but its origin was most likely in the posterior left ventricular or auricular wall.

Although we were fortunate in being able to observe the patient for nine and one-half months before his death, the correct clinical diagnosis was not made. Since the clinical and pathologic findings are similar in many respects to those of the eight striated muscle sarcomas of the heart which have been described, we have included a brief summary of each of those cases for comparison.

CASE REPORT

H. P. B., a 50 year old white, clothing salesman entered the Veterans Administration Hospital, San Francisco, on December 27, 1946, because of severe midanterior chest pain. This attack of pain had begun two weeks before, and was accompanied by nausea, anorexia, and weakness. Three days before entry the pain increased in severity, became constant, and was aggravated by exertion, cough, or deep breathing. Profuse sweats had occurred for several nights, without chills or known fever.

In 1942 the patient began having substernal chest pain, radiating to both arms and associated with dyspnea. The pain was brought on by exertion and relieved by rest or nitroglycerin. Examination at that time revealed loud systolic murmurs at the cardiac apex and base. He stopped working and had very little pain until the onset of the present illness.

On admission the patient was acutely ill, anxious, and restless. He was pale and perspired freely. The temperature was 100 F., pulse rate 80, respiration rate 20, and blood pressure 120/60. Lung fields were normal, except for a few moist râles at both bases. The heart was not enlarged and the sounds were of good quality. A loud friction rub was heard to the left of the sternum. There were no murmurs. The liver was palpable 4 cm. below the right costal margin, but the spleen was not palpable.

The pain was temporarily relieved by morphine. Although the first diagnosis was myocardial infarction, it soon became evident that the patient's course was not that of simple infarction. There were many fluctuations in the clinical course, but the overall picture was a gradual progressive decline, with increasing anorexia, weakness, and loss of weight until his death October 14, 1947, nine and one-half months after admission.

During the patient's entire hospital stay there was intermittent low-grade fever and frequent night sweats. In mid-January, 1947, a nonproductive cough developed which gradually became more severe. The precordial friction rub noted on entry became very loud and persisted for two weeks. A friction rub reappeared eight months later, associated with pain, but lasting only a few days. There was rather severe precordial pain off and on for the first three weeks, and after that occasional bouts of pain, sometimes accompanied by mild shock. Murmurs developed which changed from time to time. Two

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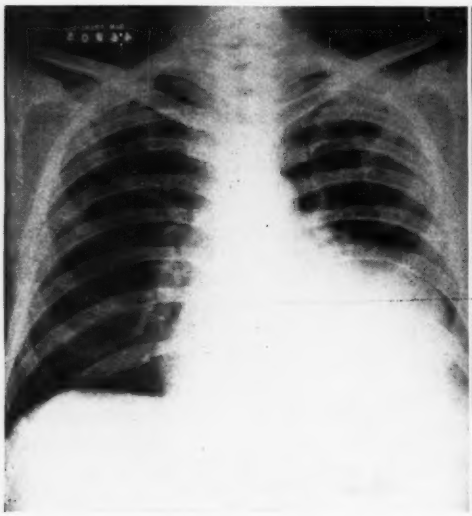
days after entry a presystolic murmur was heard, ending in a loud first mitral sound. One month later a loud systolic murmur had developed. This murmur later became less intense and then disappeared. Six months after entry, a systolic and diastolic murmur which persisted with variations in intensity was heard along the left sternal border. The spleen increased in size and became readily palpable. The liver edge remained 3 to 5 cm. below the right costal margin.

During the fourth month of illness, left hemiplegia and aphasia suddenly appeared, most likely the result of an embolus. These signs disappeared in two weeks.

aV_L and in all the V leads (fig. 3). A transient episode of auricular fibrillation with a rapid ventricular rate occurred during the second month, lasting three days. After this there were minor variations in the electrocardiogram. The last tracing made in September, one month before death, was very similar to the tracing made on admission.

Examinations of the urine revealed no significant abnormalities. The stools showed traces of occult blood on several occasions, but were otherwise normal. Blood cultures were repeatedly negative. Sputum examination for malignant cells was negative. The leukocyte count ranged from 9,000 to 13,000 per cu. mm., with normal differential counts. On



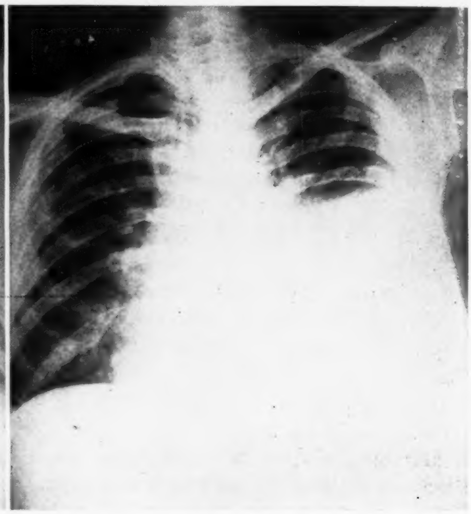


FIG. 1.—(*Left*) Roentgenogram of chest made July 7, 1947, showing a marked increase in prominence of the left border of the heart, with the outline now sharply defined.

FIG. 2.—(*Right*) Roentgenogram of chest made August 26, 1947, showing displacement of the lung upward, the tumor mass occupying the lower two-thirds of the left pleural cavity.

Six weeks after entry a density in the base of the left lung was first noted in the roentgenograms. Two months later there was evidence of partial collapse of the left lower lobe. By the eighth month of hospitalization a large mass filled the lower left side of the chest and displaced the left lung upward (figs. 1 and 2). During the fourth month several metastases were found in the right coxal bone. Subsequent studies showed similar lesions in the left coxal bone and an osteoblastic process in the bodies of the twelfth dorsal and first lumbar vertebrae.

Electrocardiographic tracings were consistently abnormal. The initial tracing showed low voltage and low or flat T waves in Leads I, II, III, aV_L, and V_5 and V_6. During the next two weeks the electrocardiographic changes were those of subacute pericarditis, with inverted T waves in Leads I and

entry the hemoglobin concentration was 10 grams per 100 cc., with 3.7 million erythrocytes per cu. mm.; a transfusion was given at that time. The sedimentation rate remained elevated at 30 to 35 mm. per hour. One month after entry the serum acid phosphatase level was 2.25 units and the alkaline phosphatase was 28.5 units (King-Armstrong). The alkaline phosphatase rose to 41.2 units in one month and later dropped to 20.7 units. The acid phosphatase remained below 3 units.

With the discovery of the bony lesions in the pelvis, the mass in the lower left side of the chest was thought to be a carcinoma of the bronchus. Toward the end the varying and unusual murmurs suggested that a primary lung tumor was invading the heart.

Abstract of Necropsy Findings

The final anatomic diagnoses were: primary myosarcoma of the heart, with extension within pericardial sac and adhesive pericarditis; partial sarcomatous replacement of posterior surfaces of both auricles and ventricles, with neoplastic vegetation on mitral valve; sarcomatous constriction of left pulmonary veins; sarcomatous metastases to left ventricular myocardium, right lung, vertebrae, and bones of pelvis; myocardial failure, with right hydrothorax, edema of legs, and pulmonary congestion; two carcinoid tumors of the ileum, with carcinoid metastases to mesenteric lymph nodes; heterotopic pancreatic tissue in the jejunum.

Thorax. A large, partially encapsulated mass, extending from the posterior and posterolateral surface of the heart, filled the lower two-thirds of the thoracic cavity on the left side, forcing the lung into the upper one-third (fig. 4). The tumor, which weighed about 2,100 grams, was composed of grayish-white spongy tissue with large areas of congestion, hemorrhage, and necrosis.

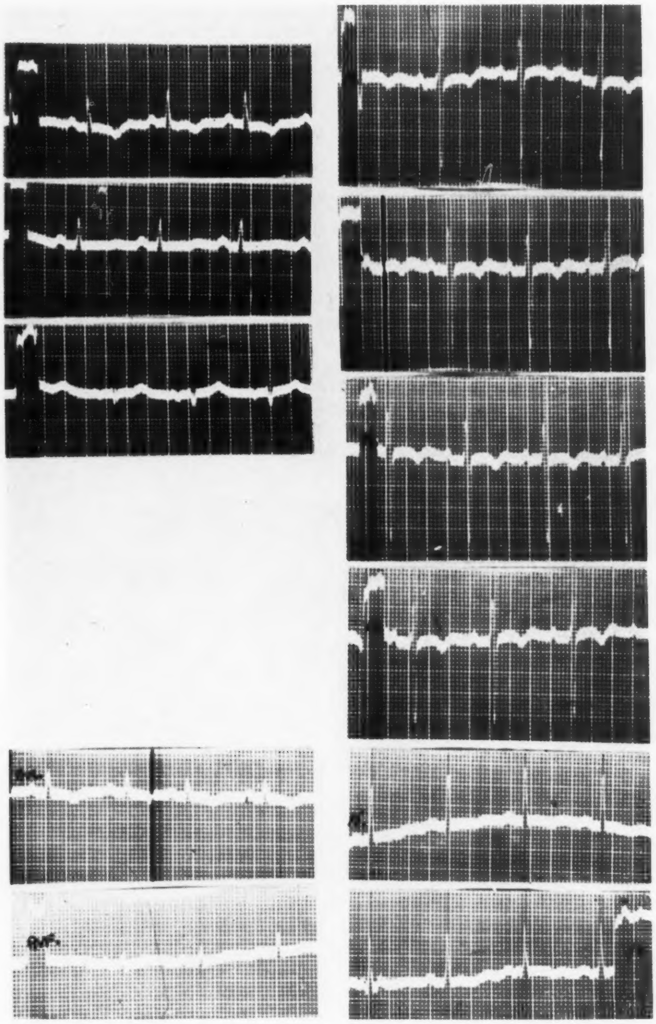


FIG. 3—Electrocardiogram made January 10, 1947. Note that the T wave in Lead I is inverted, as are T waves in Leads V_1, V_2, V_3, and V_4.

Heart. The estimated weight of the heart exclusive of the tumor was 350 grams. The pericardium was stretched over the surface of the mass. The right coronary and left circumflex arteries were normal in their proximal portions, but posteriorly were obliterated by the tumor. Just above the line of closure of the anterior mitral valve cusp was a rectangular mass of neoplastic tissue, measuring 3.0 by 2.5 by 3.0 cm., projecting from the left auricular wall over the valve opening. The mitral valve and its chordae tendineae were moderately thickened. Replacing a

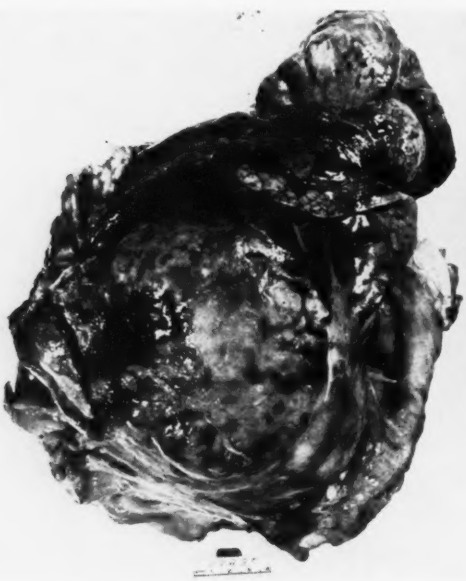


FIG. 4.—(*Left*) Photograph of the tumor mass, left lateral view. The left lung has been compressed and displaced superiorly.

FIG. 5.—(*Right*) Photograph showing the opened left ventricle and auricle. Note the tumor mass overlying the mitral valve, and tumor tissue at the upper right. The metastasis in the left ventricular myocardium is evident at the lower left.

small portion of the anterior left ventricular myocardium was a metastatic nodule, measuring 3.0 by 2.5 by 1.5 cm., composed of tissue resembling that of the large mass. The posterior portion of the myocardium of the left ventricle, a small part of the posterior surface of the right ventricle, and the posterior aspect of both auricles were partially replaced by the tumor (fig. 5).

Other Organs. In the parenchyma of the right lung were three small, grayish-white nodules, metastatic from the tumor of the heart. The left lung, which was small and atelectatic, contained no neoplastic tissue. The hilar nodes were free of metastases. The spleen was enlarged, weighing 400 grams. It contained two old infarcts which showed no evidence of tumor.

In the wall of the ileum were two small, firm, grayish-yellow nodules of neoplastic tissue, the larger measuring 1.0 cm. in diameter. In the jejunal wall was a pink nodule, measuring 1 cm. in diameter, which grossly resembled pancreatic tissue. Two small, firm, grayish-yellow lymph nodes near the origin of the superior mesenteric artery consisted mainly of metastatic tumor tissue like that of the nodules in the ileum.

The left kidney contained an old infarct, measuring 2 cm. in diameter, which contained no tumor.

In the right iliac fossa was a mass, measuring 10.0 by 5.0 by 4.0 cm., composed of homogeneous soft tissue resembling that of the heart tumor. The tumor had displaced the iliacus muscle forward and was invading the innominate bone. The bodies of the twelfth thoracic and first and second lumbar vertebrae were expanded, had a gray color, and were sclerotic.

The brain, liver, pancreas, adrenal glands, prostate gland, testes, thyroid gland, trachea, esophagus, and pituitary gland showed no significant changes.

Histopathology

The neoplastic tissue in the myocardium and intrapericardial mass, lung, metastases, and pelvic mass had the same general structure, with certain

variations. In the portion invading the myocardium, the cells varied considerably in size and shape (fig. 6, *D*). Most were large, oval cells with large nuclei, but there were many small round cells with pyknotic nuclei. Some were stellate and resembled primitive mesenchymal cells. Also present were many large tumor giant cells, as well as small numbers of strap-like, elongated cells, with oval nuclei, which resembled muscle fibers but lacked transverse striations. These in some areas formed syncytial strands, with a suggestion of branching. All of the cells had abundant, deeply eosinophilic cytoplasm with many small vacuoles. The mass above the mitral valve was composed mainly of fibrin, with widely dispersed, spindle-shaped, neoplastic cells.

The cells of the metastases were much better differentiated toward mature muscle fibers. In the lung, for example, the metastases were composed mainly of long, ribbon-like cells with elongated, oval nuclei, with delicate chromatin, many containing prominent eosinophilic nucleoli (fig. 6, *A*, *B*, *C*). There were smaller numbers of round cells, but many large tumor giant cells were present like those in the intrapericardial mass. The tumor cells in the lung were arranged in bundles with slight whorling. The cells of the metastases in the pelvis and vertebrae resembled those of the lung metastases. Connective tissue stains revealed occasional longitudinal fibrils but no distinct transverse striations.

Gastro-enteric Tract. The small mass in the jejunum occupied almost the entire thickness of the bowel wall, being covered on one surface by mucosa and muscularis mucosae. It was composed of normal pancreatic tissue, traversed by strands of muscle. The two nodules in the ileum were composed of neoplastic tissue, typical of carcinoid tumors, which replaced the submucosa and much of the muscle, extending centrally to the mucosal epithelium. The tumor cells were small and uniform, with round vesicular nuclei and a small amount of granular cytoplasm with indistinct borders. The cells were closely grouped to form small masses around central capillaries, separated by narrow fibrous strands. In one of the nodules in the ileum the tumor was infiltrating the serosa. One mesenteric node showed complete replacement of its normal structure by carcinoid tumor.

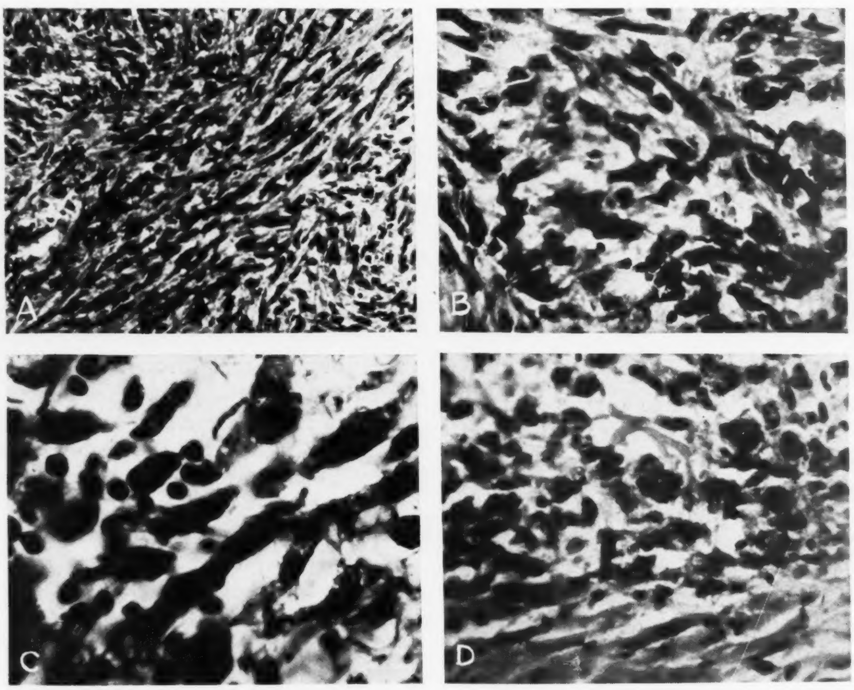


FIG. 6.—*A*, *B*, and *C*: Photomicrographs at increasing magnifications of the lung metastases, showing the fusiform and ribbon-like cells. *D*: Photomicrograph of left ventricular myocardium, showing tumor cells invading the muscle. Note the multinucleated cells.

Discussion

Study of the few muscle tumors of the heart which have been described leaves their origin obscure. The association of such a tumor in this case with pancreatic heterotopia suggests that it may have arisen from a congenital rest of muscle, possibly in the wall of the left auricle. Larson and Sheppard,[11] in a case more fully described below, found a rhabdomyoma of the left auricle, with sarcomatous extensions, and considered that the rhabdomyoma had undergone malignant change. Júnior[9] described a rhabdomyosarcoma of the heart in which all stages of development of cardiac muscle were represented, from primitive myoblasts to cells with distinct transverse striations. A horseshoe kidney was found in his case, and the author felt that the presence of this congenital renal anomaly was evidence that the heart tumor had arisen from a congenital rest.

Classification of striated muscle tumors has been confused by disagreement on the importance of demonstrating striations. Cappell and Montgomery[3] divided these tumors into (1) those showing well defined cross striation and (2) those in which cross stiiation is lacking. They subdivide the first group into: (a) simple rhabdomyomas and (b) malignant rhabdomyomas, showing well defined cross striations in at least a small proportion of cells. The second group consists of cells morphologically resembling myoblasts, either showing very delicate striations or completely devoid of striations. The tumor encountered in our case falls into the last group.

Reported Cases of Striated Muscle Sarcoma of the Heart

The first case, reported by Bradley and Maxwell[2] in 1928, occurred in a 62 year old man, ill for only seven or eight weeks. The chief symptoms and signs were pain in the upper left side of the chest, swelling of the face and neck, fever, marked dyspnea, and anemia, with 40 per cent hemoglobin. The heart was greatly enlarged roentgenologically. At autopsy, a tumor was found which filled the pericardial sac and invaded the heart muscle. There were metastatic nodules in the myocardium of the septum and left ventricle, lungs, liver, and kidneys. The tumor was composed of striated cells, giant cells, and long spindle cells with eosinophilic cytoplasm. The cells of the metastatic nodules were better differentiated than those in the primary lesion.

Müller,[16] in 1932, reported a case of rhabdomyosarcoma of the left auricular wall. No clinical information was included in the report. The tumor consisted of large, striated spindle cells of various sizes, with long nuclei. In the left auricle was a "pseudo-myxoma" which was thrombotic. There were metastases in the left lung, pancreas, and small bowel, as well as infarcts of the spleen, kidney, and brain.

A primary rhabdomyosarcoma of the heart, appearing in a 62 year old woman, was reported by Barnes, Beaver, and Snell[1] in 1934. The chief symptoms were pain in the thorax and dyspnea on exertion. There was a pericardial friction rub, and the patient developed complete heart block. A metastasis to the left deltoid muscle was present. At autopsy, diffuse involvement of the right auricle and ventricle with tumor nodules was encountered, with small metastatic nodules in the lungs, mesenteric lymph nodes, and adrenal glands.

A case of rhabdomyosarcoma, occurring in a 16 year old girl, was described by Reeves and Michael[18] in 1936. The patient had been ill for only six days with dyspnea, abdominal pain, and marked fatigue. For the previous year she had complained of easy fatiguability. Physical examination revealed moist râles throughout both lung fields, pulse rate 140 per minute, and distant heart sounds. At autopsy, both auricles were almost completely replaced by a friable, hemorrhagic, soft, nodular tumor mass, which ruptured into the pericardial cavity posteriorly. It was composed of small and large spindle cells, with fairly numerous giant cells. There were no metastases.

Larson and Sheppard,[11] in 1938, described a primary tumor of the heart in a 37 year old woman. A polypoid tumor mass hung down from the left auricular lateral wall into the left ventricle. There was a small isolated rhabdomyoma in the adjacent portion of the left auricular wall. The tumor, which extended into the base of the lung near the hilus, appeared sarcomatous in its extensions.

A case similar to ours in certain respects was reported by Júnior[9] in 1942. When first seen

the patient, a 39 year old white man, had numerous tumor nodules in the subcutaneous tissues. He soon died in coma, after a febrile course with anorexia, emaciation, general weakness, and pain in the back and limbs. Autopsy revealed a polypoid, soft, red tumor mass in the left ventricular cavity, attached by a pedicle to the anterior wall. The adjoining myocardium was invaded. Metastases were found in the subcutaneous tissues, brain, lungs, bronchial lymph nodes, liver, kidneys, and intestine. The tumor, which looked the same everywhere, was composed of cells in bundles and syncytial strands, with eosinophilic cytoplasm. There were many vacuolated giant cells. Many of the elongated cells had longitudinal striations, with occasional transverse striations. Coincidental findings were a supernumerary spleen and a horseshoe kidney with dilated pelves.

Wells, Rowe, and Jaffe[20] in 1947 reported a myosarcoma occurring in the heart of a 15 year old boy who had been apparently well until five days before death. His symptoms were pain in the chest, abdominal distress, fatigue, and difficulty in breathing. When examined, the patient was dyspneic and in shock, with weak, distant heart sounds. A diastolic apical murmur was heard on one examination. A pericardial friction rub was heard on the first day of illness, disappearing later. The electrocardiographic findings were: rapid rate; regular rhythm; depressed RS-T segments in Lead II; upright T waves in Leads I, II, and IV; and inverted T wave in Lead III. Autopsy revealed a large, hemorrhagic, friable, pedunculated tumor mass attached to the area of the foramen ovale in the right auricle, filling the tricuspid orifice and right ventricle. The hemorrhagic, necrotic tumor was composed mainly of spindle-shaped cells, with some multinucleated cells.

Leach,[12] in 1947, described a case of primary rhabdomyosarcoma of the heart in a 14 year old boy. He had been seen first in May, 1936, because of coughing, more severe on lying down, and increasing fatigue of three weeks' duration. Roentgenograms revealed a bulging mass in the superior mediastinum. Roentgen-ray therapy was given for three weeks. When seen again in July, 1938, the patient was moribund and soon expired. At autopsy a large mass was found in the mediastinum, replacing the thymus and extending down to a short distance above the diaphragm. The right ventricle was filled with a polypoid tumor mass, composed of ribbon-like cells with eosinophilic cytoplasm, some with longitudinal striations. The heart tumor was not as well differentiated as the mediastinal mass.

Comment

Although cardiac tumors produce no characteristic signs or symptoms, such tumors have occasionally been correctly diagnosed. It is sometimes difficult to correlate the clinical and pathologic features. Very large intracardiac tumors may produce surprisingly few symptoms for a long period of time. The clinical course is often that of cardiac decompensation, resulting from extensive myocardial replacement, obstruction of valve orifices, or pericardial effusion. Changing heart murmurs similar to those in our case have been noted often. Pedunculated tumors sometimes drop through the valve and simulate valvular disease, producing signs which may vary with changes of posture. The mass over the mitral valve in our case did not produce this effect. Emboli from vegetative valve lesions may produce symptoms, such as the transient hemiplegia in our patient. Anginal attacks result from obstruction of the coronary arteries. Roentgenologic changes in the silhouette of the heart sometimes appear early.

Arrhythmias are common, complete heart block or bundle branch block often resulting from invasion of the interventricular septum. However, even with such invasion there may be no alteration of rhythm from the normal. Transient fibrillation such as our patient manifested has been noted before. Fishberg,[6] discussing auricular fibrillation and flutter in metastatic growths of the right auricle, reported two cases of cardiac tumors in which arrhythmia persisted, after onset, until death. In his third case, however, the patient developed flutter fifteen days before death, reverting to normal rhythm in three days. Hamilton-Paterson and Castelden[8] have described a case of round-and-spindle-cell sarcoma of the right auricle in a 45 year old woman in whom auricular fibrillation was noted about four months before death. Four weeks later the rhythm returned to

normal, auricular fibrillation recommencing about a month before death.

Pericardial effusions, recurrent and frequently hemorrhagic, often occur in association with primary and secondary tumors of the heart or pericardium. Mahaim[15] has stated that hemopericardium is the most important sign of malignant tumors of the heart and of benign and malignant tumors of the pericardium.

The straplike shape of the cells of the heart tumor, their strongly acidophilic cytoplasm, the formation of syncytial strands, and the occurrence of large vacuolated giant cells indicate that the neoplastic cells were differentiating towards striated muscle. Longitudinal fibrils were seen in some cells. As in certain of the cases summarized above, the tissue of the primary neoplasm was not as well differentiated as the tissue of its metastases.

In describing a fibrosarcoma of the heart, Woll and Vickery[22] commented that theirs was the first primary tumor of the heart metastasizing to the vertebrae. In our case, metastases in the bones directed attention to the chest, and repeated roentgenograms revealed a tumor mass in the lower left thorax. The tumor was thought to be primary in the lung, involving the heart, but instead, was primary in the heart, displacing the left lung.

Summary

A case is reported in which a primary myosarcoma of the heart, metastasizing to the right lung, ilium, and vertebrae, occurred in conjunction with heterotopic jejunal pancreatic tissue and carcinoid tumors of the ileum, the latter metastasizing to mesenteric nodes. The previously reported cases of striated muscle sarcomas of the heart are briefly reviewed.

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Primary Tumor of the Pericardium Involving the Myocardium: Surgical Removal

By Lew A. Hochberg, M.D., and Alexander I. Robinson, M.D.

A case is presented in which a primary tumor of the pericardium, with myocardial involvement, was discovered at the time of surgical exploration. The tumor was removed and the patient has remained well and active at the time of this report, eighteen months after the operation.

PRIMARY tumors of the heart and pericardium are rare. In a series of 480,331 autopsy subjects examined between 1938 and 1942, collected by the American Medical Association, there were only eight primary tumors of the heart—a necropsy incidence of 0.0017 per cent (Strauss and Merliss[1]). This is apparently a much lower incidence than is cited in the literature. The frequency of these tumors is usually given as about one in every 8,000 or 10,000 necropsy studies or an autopsy incidence of about 0.012 per cent. According to Perlstein[2] the earliest recorded primary tumors of the heart were those reported by Boneti in 1700 and Morgagni in 1762. According to Gottel[3] the first case in which a correct antemortem diagnosis of such tumor was made was the one reported by Pawlowski. Shelburne[4] made a similar and correct antemortem diagnosis of primary tumor of the heart in 1935. In 1930, Keller and Callender[5] reported the successful removal of a "neurofibroma arising on the pericardial pleura" which was attached to the pericardium by a broad base, over the course of the phrenic nerve. In removing this tumor a fringe of invaded lung tissue was also removed. The patient was well eighteen months after the operation. The following year, Everingham[6] removed a primary endothelioma of the pericardium but the patient died nine days after the operation. The first and only report of the surgical removal of a primary tumor of the heart was that made by Beck[7] in 1942. In this article Beck also reports another patient from whom he successfully removed a cystic intrapericardial teratoma. In 1945, Mahaim[8] published a review of the cases of primary tumors of the heart and pericardium. He was able to collect 329 tumors of the heart and 84 of the pericardium—making a total of 413 neoplasms. In the three years following the publication of this report there were an additional 13 cases reported in the literature. In 1915, Timme[9] reported a case of cavernous hemangioma of the pericardium—one similar to that reported by Lefas in 1898. A review of the literature after 1915 reveals 2 additional cases of cavernous hemangioma of the pericardium.

We are reporting the surgical removal of a primary tumor of the pericardium, first because the condition is so uncommon, second because this is the fifth case of a cavernous hemangioma of the pericardium on record and the first case in which such a tumor was removed surgically, and finally to point out that cure is possible if the patient is submitted to surgery before there is impairment of cardiac function.

Case Report

F. S., an 8 year old girl, entered Bushwick Hospital on August 22, 1948, because of increasing fatigue during the previous two months. In this period her appetite had become poor and her interest in active play waned so that she preferred to remain inactive. The mother also noticed that the child was moderately dyspneic on slight exertion.

The patient was born at full term by spontaneous delivery and was normal at birth. She had whooping cough at 18 months of age and thereafter did not gain weight too readily. Except for frequent upper respiratory infections she was apparently normal until about two months prior to the discovery of her intrathoracic condition. In June of 1948 she was

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seen by the family physician because of an upper respiratory infection and tonsillitis. Upon her recovery, the physician advised tonsillectomy. However, before subjecting the child to an operation a routine check-up was made. Fluoroscopic examination of the chest revealed an enlargement of the cardiac shadow to the right.

On admission to the hospital it was noted that the child was very pale, undernourished, and somewhat dyspneic on moving about in bed. There were no visible pulsations in the neck or on the chest wall. The pulse in both arms was equal in rate (120 per minute), rhythm, and volume. The left lung appeared normal on percussion and auscultation. The

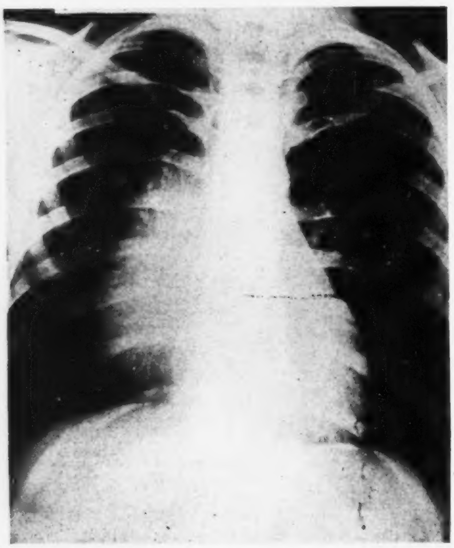

FIG. 1.—Preoperative posteroanterior roentgenogram of the chest showing an opacity along the right side of the heart, extending from the level of the first anterior rib down to the diaphragm.

area of cardiac percussion dullness was enlarged to the right. There were no abnormal heart sounds heard. The breath sounds on the right side of the chest anteriorly were absent in the paracardiac region and essentially normal throughout the other areas of the right lung field. Results of the remainder of the physical examination was noncontributory. Fluoroscopic examination of the chest revealed an opacity in the right anterior paracardiac area which was intimately connected with the heart. The opaque area transmitted cardiac pulsations rather feebly and en masse. Roentgenograms of the chest in the posteroanterior and lateral projections revealed an ovoid mass to the right of the heart, in the anterior half of the chest, which extended downwards from the region of the first rib anteriorly to the diaphragm. The mass was intimately connected to the heart (fig. 1). The preoperative diagnosis rested between (1) a pericardial cyst and (2) an anterior mediastinal tumor the nature of which could not be determined.

On August 24, 1948, an exploratory thoracotomy was performed under endotracheal anesthesia. The right side of the chest was opened through a posterolateral approach via the periosteal bed of the resected fifth rib. After entering the thoracic cavity the right lung was displaced posteriorly and a mass noted anteriorly which projected into the right pleural cavity. The growth was covered by mediastinal pleura. The latter was opened and the tumor mass explored. The neoplasm covered the right side of the heart and to a lesser degree enveloped the anterior and posterior aspects of the heart. The tumor extended from the region of the entrance of the superior vena cava into the right auricle down to the diaphragm anteriorly. The growth was irregularly firm and cystic and measured about 5 inches in its longest diameter. It was fused to the underlying right auricle and the overlying thymus was attached to the tumor. The mass was readily lifted off the pericardium inferiorly but superiorly and anteriorly this could not be accomplished. The pericardial sac was opened and the tumor separated from the myocardium by alternate blunt and sharp dissection. As the orifice of the superior vena cava was approached it was deemed necessary to remove the tumor with some of the adherent myocardium. Accordingly, the tumor was shaved off the muscle. At this time it was noted that the tumor masses on the pericardium and myocardium were really one structure and that the neoplasm had grown through the pericardium. Upon separating the tumor from the heart some bleeding from the myocardium occurred. This was controlled by one suture over a piece of oxidized cellulose. The tumor was then everted and separated from the thymus. However, a fringe of thymus also had to be removed. As the tumor was being separated from the pericardium posteriorly it was noted that the left mediastinal reflection of pleura was also adherent to the tumor, necessitating removal of part of the pleura and opening into the left pleural cavity before the tumor could be freed. Upon removal of the tumor, the anesthetist maintained anesthesia under increased pressure, thereby reducing the pneumothorax on the left side. A small rubber tube was then placed in the right pleural cavity, against the opening in the mediastinum, and exteriorized through the anterior part of the skin incision. The wound was then closed in layers. As the intercostal muscles and pleura were being approximated, the lung was inflated to a state of almost complete expansion. When all sutures were tied and the pleural cavity sealed, the tube in the chest was closed off. The other tissues were then approximated in layers. The immediate postoperative reaction was good. Upon the patient's return to

FIG. 2.—The tumor (closed) after removal.

FIG. 3.—The tumor (opened) showing some of the cystic areas.

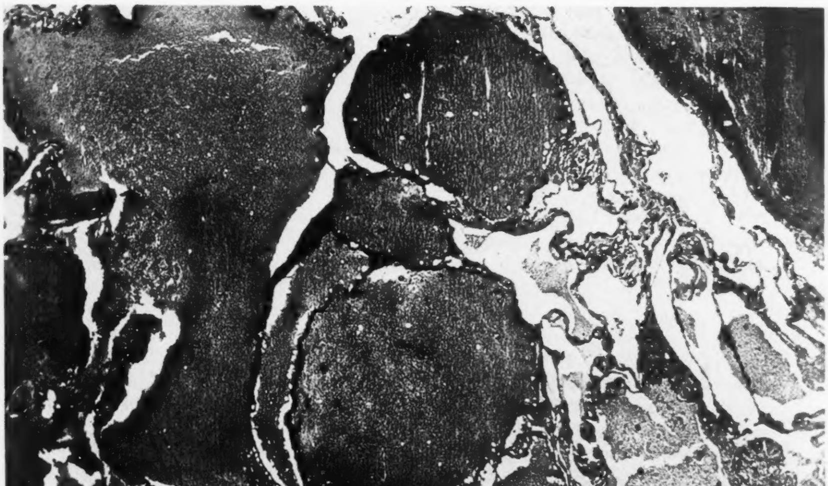

FIG. 4.—Photomicrograph of a section from the tumor (magnification 48×)

the ward the tube in the chest was immediately attached to a subaqueous drainage apparatus.

The day after the operation the patient's temperature rose to 101 F. and remained at this level for the next two days. During these two days the child was not very dyspneic or cyanotic. A roentgenogram of the chest made with the patient in the erect position on the evening of the second postoperative day revealed some fluid in the right pleural cavity and a partial pneumothorax on the left side. On the third postoperative day the child was somewhat more dyspneic than heretofore (temperature 101 F., pulse rate 110 per minute, and respiration rate 46 per minute). The left pleural cavity was aspirated, with removal of about 60 cc. of air. The following day the child's condition began to improve and the temperature, pulse rate, and respiration rate began to return to normal values. On the fourth day after the operation the drainage tube was removed. A roentgenogram on the fifth and sixth postoperative days (made with the child in the reclining position) showed a thin layer of fluid in the right pleural cavity and a residual pneumothorax on the left side. The patient improved steadily after the fourth day and was discharged from the hospital on the thirteenth postoperative day.

The pathologist's report on the gross appearance of the tumor was as follows: "The specimen consists of an oval mass of soft tissue, 9 by 6 by 3.5 centimeters. Most of the outer surface is smooth and shiny. Beneath the surface are visible slender and broad spaces containing fluid blood. Parts of the surface are covered with strands of light-yellow adipose tissue and are devoid of the delicate transparent membrane which covers the remainder of the specimen. The cut surfaces disclose many communicating spaces 0.1 cm. to 2 cm. in diameter separated by delicate strands of transparent membranes. In places, the spaces are prominent and the septa scanty. In other places, the septa are heavier and the spaces are small, or the tissue is more solid and the spaces are few. An occasional kernel of hard pale-yellow material is present within a small space or enveloped by the septa. Where the tissue is more solid, there is present also light-yellow adipose tissue (figs. 2 and 3).

"On microscopic examination, various-sized spaces containing blood are noted, separated by delicate strands of connective tissue or by broader septa of smooth muscle or by areas of adipose tissue. Most of the spaces are lined by a single row of flat cells. Some of those surrounded by bundles of smooth muscle fibers resemble large irregular veins. In places, the septa contain accumulations of small round cells and large mononuclear cells. One of the yellow kernels noted grossly presents a circular structure of pink-staining amorphous material enclosed in a broad band of concentric layers of hyalinized fibrous connective tissue. Some of the blood spaces contain smooth round masses of clotted blood traversed by strands of long, slender cells which stream out from a small area of attachment to the lining of the blood spaces (Fig. 4).

"Diagnosis: Hemangioma, cavernous."

At the present time, eighteen months after operation, the child is well, has been active in her school work for several months, and has not had any recurrence of symptoms. Roentgenographic examination of the chest at monthly intervals shows no signs of recurrence of the disease.

Summary

A brief review of primary cardiac and pericardial tumors is presented with a case report of a primary tumor of the pericardium in which instance the neoplasm was removed surgically.

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Congenital Arteriovenous Fistulas of the Thoracic Wall

By HERBERT C. MAIER, M.D., AND ARTHUR PURDY STOUT, M.D.

Arteriovenous fistulas of the thoracic wall may produce murmurs and thrills which suggest an intrathoracic vascular abnormality. Congenital arteriovenous fistulas in the precordial region, the site of the fistula in the case here reported, may be confused with anomalies of the heart and great vessels. The differential diagnosis of blood vessel tumors of the chest wall is discussed. Occasionally arteriovenous fistulas involve both the thoracic wall and intrathoracic viscera.

CONGENITAL arteriovenous communications within the structures of the thoracic wall are uncommon. Such lesions are of interest to the cardiologist, however, since occasionally they may be confused with intrathoracic vascular abnormalities. Moreover, the pathologic process may involve both the chest wall and the intrathoracic viscera, either as a single or as separate lesions.

If a congenital arteriovenous fistula in the precordial region causes a continuous murmur and thrill, the clinical features may simulate those of a cardiac lesion. A patent ductus arteriosus had been the original diagnosis in a case which we are reporting, but a few years later, when a mass was palpable in the chest wall, it was realized that the lesion was extracardiac.

CASE REPORT

R. M., a woman, was 30 years old on admission to Lenox Hill Hospital in January 1947. Twelve years previously, when she was examined while attending college, a murmur was heard in the precordial region and a patent ductus arteriosus was diagnosed. Five years later, the patient palpated a soft mass underlying the inner portion of the left breast and became conscious of occasional throbbing in that region. The area was slightly tender on pressure. A diagnosis of aneurysm of an intercostal or internal mammary artery was made by Dr. Ernst Boas. Operation was recommended but was not carried out at that time.

The prominence of the inner portion of the left breast increased very slightly during the next seven years. The mass, which was quite inconspicuous, became more evident when the patient was excited. There had never been any cardiac symptoms. There was no history of trauma.

Physical examination revealed a well developed and well nourished woman in apparent good health. There was no cyanosis or clubbing of the fingers. The breasts were symmetrical but there was a slight rounded prominence in the medial portion of the left breast. The overlying skin showed no discoloration. Palpation revealed a continuous thrill which was diminished by firm pressure at the level of the third intercostal space just to the left of the sternum. On auscultation there was heard a loud, continuous, rough murmur with systolic accentuation, which was transmitted out to the left. There were no other abnormal findings over the rest of the precordium. The blood pressure was 130/80. The remainder of the physical examination, including fluoroscopy, revealed no abnormality. There was no cardiac enlargement. Roentgenogram in lateral projection showed questionable evidence of phleboliths in the region of the lesion. A preoperative diagnosis of congenital arteriovenous fistula of the internal mammary vessels was made. Operation was performed on January 18, 1947.

An incision was made in the region of the second costal cartilage which was resected. The internal mammary vessels were exposed at this site and found to be several times larger than normal. The artery and vein were ligated and divided with resultant diminution in the thrill and pulsation in the upper mesial portion of the vascular mass. Dissection was then carried downward and other branches from the internal mammary vessels entering from the medial aspect were divided. One large vessel perforated the intercostal muscle just lateral to the sternum and was ligated superficial to the intercostal muscle. The skin incision was extended and the breast, which was uninvolved, was reflected downwards and laterally. The lateral portion of the pectoralis major muscle was thus exposed. Two

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Figs. 1 and 2 (See facing page)

large pulsating vessels could be felt entering this muscle in the axillary region. These vessels were abnormally large branches of the acromiothoracic and lateral thoracic arteries. After ligation of these vessels, the pulsations ceased. The pectoralis major, which contained the mass of blood vessels, was then excised except for the uninvolved clavicular and axillary portions. At operation the gross findings were interpreted as those of a cavernous hemangioma of the pectoralis major muscle. The breast was replaced and sutured in position. The postoperative course was uneventful. The patient was well when seen two years after operation and there were no signs of recurrence.

Pathologic Findings. On gross serial section of the operative specimen a number of thick-walled dilated blood vessels were found scattered through the central portion of the muscle. A microscopic section cut longitudinally paralleling the fibers of the muscle showed a group of arteries and veins. The arteries were conventional in the arrangement of muscle and elastic tissue save for the occasional thickening of the subintimal tissues and interruption of the internal elastic lamina by fibrosis. The veins were for the most part thick walled and fibrous—similar in structure to varicose veins. There was one unusual feature: although the muscularis was not hypertrophic and did not have the appearance of arterial muscle, there was in places an internal elastic lamina which had some resemblance to the arterial type. This was found at one part of a long tortuous vein and was absent at the other. The two parts were joined by a very narrow communication. The appearance suggested a fistulous communication (fig. 1). In another area, two thick-walled veins were shown with a marked proliferation of capillaries, arterioles, and venules between them (fig. 2). The whole picture suggested the formation of fistulous communications between arteries and veins with some tendency for the elastic tissue of one vein to approximate the appearance of the internal elastic lamina of an artery. There had also occurred a tumor-like proliferation of capillaries, venules, and arterioles—a phenomenon which has been noted in other cases of congenital arteriovenous fistulas.

Discussion

At the time of operation a diagnosis of cavernous hemangioma of the pectoralis major muscle was made. On microscopic examination of the lesion this diagnosis was proved to be incorrect. A cavernous hemangioma is a vascular tumor composed of blood vessels of the order of capillaries enlarged into cavernous spaces filled with blood. No such formations were seen in our specimen. The possibility of cirsoid aneurysm and venous racemose aneurysm may both be excluded as well. The former is composed exclusively of a congeries of vessels of the order of arteries and the latter exclusively of veins. In our case a congeries of large vessels was present but both arteries and veins were represented with probable fistulous communications between them. In addition there was a proliferative conglomeration of small vessels including capillaries, arterioles, and venules.

An arteriovenous fistula may occur in various structures of the chest wall. Often more than one tissue is involved. If the vascular mass lies within a skeletal muscle, differentiation between cavernous hemangioma of muscle and arteriovenous fistula may not be apparent on gross inspection.

Hemangiomas of skeletal muscle are relatively uncommon and muscles of the trunk are rarely involved. Shallow and his associates[3] collected 335 cases of hemangioma of striated muscle from the literature. In this group there were only 63 cases in which the muscles of the trunk were involved and 39 of these hemangiomas occurred in the chest wall. Hemangiomas are most common in the muscles on the posterior aspect of the thorax. Only 6 cases of hemangioma of the pectoralis major muscle have been reported. In 2 of these the adjacent muscles and skin were involved.

Acquired arteriovenous fistulas, chiefly as the result of a penetrating wound, are far more common than congenital lesions. Occasionally it is not possible to differentiate between those of congenital and those of traumatic origin, especially in cases of nonpenetrating injuries. An arteriovenous communication is rarely established through erosion of the blood vessels

FIG. 1.—(Upper illustration) Low-power photomicrograph made through the pectoralis major muscle, fibers of which are shown above and below. Between them are the large vessels; the rounded ones are arteries cut in cross section and the longitudinal ones are thick-walled veins. Near the right-hand end a large vein communicates by an exceedingly narrow lumen with a larger vessel which is venous in aspect but has an incompletely developed internal elastic lamina.

FIG. 2.—(Lower illustration) Low-power photomicrograph showing two thick-walled veins and between them a massive circumscribed proliferation of capillaries, venules, and arterioles.

by an inflammatory or neoplastic process. The infrequency of traumatic arteriovenous fistula of the chest wall as compared with traumatic intrathoracic arteriovenous communications is indicated by Schumacker's statistics.[4] Of 354 traumatic arteriovenous fistulas and arterial aneurysms only a single one involved a vessel of the chest wall; this was an arteriovenous fistula of the internal mammary artery. Neoplasms involving the chest wall, especially the sternum, may occasionally manifest considerable pulsation and thus be confused with aneurysms and arteriovenous fistulas. Metastatic carcinoma of the thyroid gland and hypernephroma are the neoplasms most likely to present such a clinical picture. Marked vascularity of the tumor mass usually accounts for the pulsation. When a tumor or inflammatory process causes destruction of the sternum, a pulsation may be transmitted from the large underlying vascular structures in the mediastinum.

Since intrathoracic aneurysms with projection into or through the chest wall are more common than pulsating vascular masses arising in the thoracic parietes, aneurysm of the aorta or of other large vessels is usually to be considered first in the diagnosis. Fluoroscopy and angiocardiography may be of great aid in the differential diagnosis.

Arteriovenous communications in the deeper layers of the chest wall may cause notching of the lower borders of the ribs such as is usually associated with coarctation of the aorta. Similar rib notching resulting from the collateral circulation has been observed in a case of tetralogy of Fallot without coarctation of the aorta.

Arteriovenous fistulas of the thoracic wall may be confused with intrapulmonary arteriovenous fistulas. Most patients with the latter lesion also have small hemangiomas in the skin and mucous membranes. The characteristic features of a pulmonary arteriovenous fistula are cyanosis and polycythemia associated with roentgen-ray evidence of one or more lesions in the lungs. Cyanosis and polycythemia are occasionally absent. A continuous murmur may be heard over the area of the lesion in the lung. Angiocardiography establishes the diagnosis. Surgical removal of the involved portion of the lung cures the pulmonary lesion.[2] Clagett and Burchell[1] reported a case of pulmonary arteriovenous fistula of the right middle lobe associated with marked enlargement of the internal mammary artery and veins. Owing to the large quantity of blood which entered the lung from the vessels in the thoracic wall, the lobe became more and more congested as the hilar structures were ligated during operation. Separation of the lobe from the chest wall was accompanied by severe bleeding. One of us has observed a patient with arteriovenous fistulas in the chest wall on one side and apparently an arteriovenous fistula in the lung on the other side causing hemoptysis. This patient also had notching of the ribs on the side of the arteriovenous communication in the chest wall.

Summary

Congenital arteriovenous fistulas in the thoracic wall may simulate intrathoracic vascular lesions. A case of arteriovenous fistula in the precordial region which originally presented physical signs suggestive of patent ductus arteriosus is reported. The lesion was successfully removed by operation.

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Diverticulum of the Pericardium

By Louis Faugeres Bishop, Jr., M.D., Paul A. Kirschner, M.D., and Theodore Pessar, M.D

A case of true diverticulum of the pericardium is reported, with a review of the literature. A cure was effected by excision of the cystic pericardial diverticulum. Consideration of the etiology of true pericardial diverticulum is given, and possible explanation for accumulation of the fluid is suggested.

WE ARE reporting a case of pericardial diverticulum, as much for a consideration of its cause as for additional documentation of this rare condition.

In the American literature, Mazer[1] was the first to report an instance of true pericardial diverticulum proved by operation or autopsy. Cushing[2] collected the published reports of 39 cases, adding one of his own, and Reitan[4] (quoted by Haas[3]), enumerated 55. Specifically, Cushing[2] failed to differentiate true from false diverticula, or to mention embryologic background; his own case was apparently of an inflammatory nature. Reitan,[4] on the other hand, grouped his cases into acquired and congenital types, the former being encapsulated pericardial exudates, while the latter (the minority) were noninflammatory or true diverticula. Mazer[1] recognized the same distribution in the literature up to that time. Our case, in its essential features, fits into the category of true pericardial diverticula.

Case Report

A 26 year old tugboat hand was admitted to the Veterans Administration Hospital, Bronx, N. Y., on March 26, 1948, because of easy fatiguability of five months' duration, and a recent history of pain in both flanks. The pain was dull in character. Originating in the costovertebral regions, it radiated anteriorly, in girdle fashion, about the lower chest on both sides to the midepigastrium. Pain first occurred in the early morning, approximately two weeks before hospitalization, and lasted half an hour, disappearing spontaneously. It had occurred on three successive mornings after its onset, with no further recurrence. The patient had been doing heavy labor up to the time of admission without undue distress.

At the time of the onset of the pain, the patient went to a clinic where x-ray examination of the chest was made. He was told that he had "a swelling on his heart," and hospitalization was advised.

The past history indicated that he had suffered an attack of acute polyarthritis at the age of 13 years, which had necessitated absolute bed rest for a period of three months. A year following this episode, he was told that he had a "heart murmur." He passed the Army physical examination in 1943, and subsequently had had several careful physical examinations for the Paratroopers and Rangers, with no abnormality noted.

On admission to the Veterans Administration Hospital, physical examination failed to reveal any physical abnormality. Laboratory studies included a Kahn test, complete blood count, determination of blood sedimentation rate, and urinalysis. Results of none of these studies indicated any abnormality. An electrocardiogram made on admission also showed no abnormality. The x-ray and fluoroscopic study of the chest revealed the heart to be enlarged in the transverse diameter. There was a localized bulge in the region of the left ventricle, which appeared to move independently of the left ventricle (fig. 1). The localized bulge seemed to be cystic in nature, changing its configuration on inspiration. The apparently localized cystic lesion seemed to be adherent to the left ventricular wall. Angiocardiogram failed to reveal opacification of the mass (fig. 2).

Clinical Course. The patient was admitted to the Cardiac Service, and a tentative diagnosis of pericardial cyst was made. He was asymptomatic, except for occasional vague pain on the left side of the chest.

He was transferred to the Chest Surgical Service. On April 30, 1948, a left intercostal thoracotomy was accomplished, and a cystic mass measuring approximately 2 inches in its greatest diameter was found. The mass was covered by a layer of parietal pleura. When dissected free down to its base, it was found to communicate with the pericardium by means of a narrow neck measuring approximately 2 to 3 mm. in diameter. The cyst contained clear, watery fluid. It was easily separated from the pericardium down to its neck, where it was divided, at

From the Veterans Administration Hospital, Bronx, N. Y.

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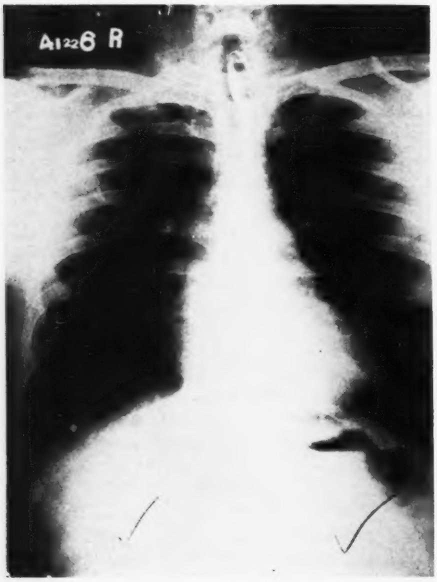

Fig. 1.—Esophagram (anteroposterior view) made on March 26, 1948, shows a localized bulge in the region of the left ventricle.

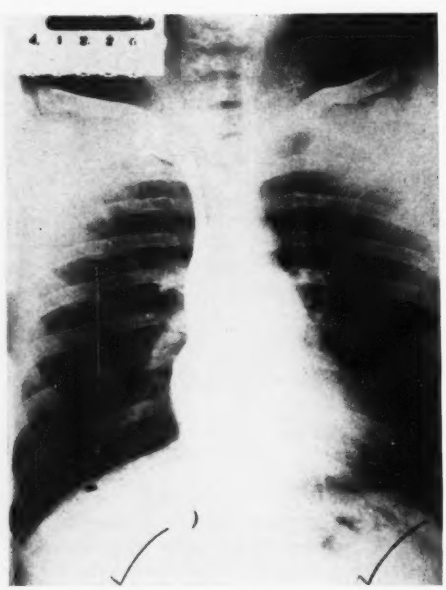

Fig. 2.—Angiocardiogram (anteroposterior view) made on March 31, 1948, reveals nonopacification of a mass adjacent to the left ventricular wall.

which point its attachment to the pericardium was demonstrated. The cystic diverticulum was then excised.

The postoperative course was uneventful. Immediately following operation, the electrocardiogram showed an inverted T wave in Lead CF$_4$; tracing made on May 11, 1948, showed reversion of the T wave in Lead CF$_4$ to normal. Postoperative x-ray examination on May 3, 1948, revealed a normal cardiac contour, and the oval density was no longer discernible (fig. 3).

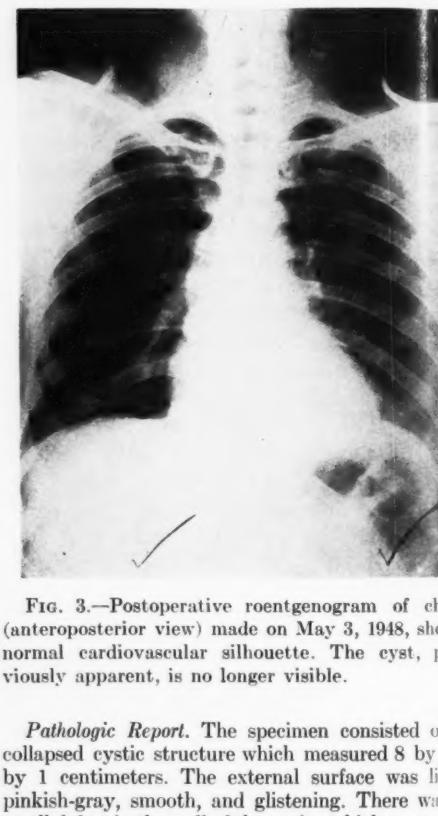

Fig. 3.—Postoperative roentgenogram of chest (anteroposterior view) made on May 3, 1948, shows normal cardiovascular silhouette. The cyst, previously apparent, is no longer visible.

Pathologic Report. The specimen consisted of a collapsed cystic structure which measured 8 by 4.5 by 1 centimeters. The external surface was light pinkish-gray, smooth, and glistening. There was a small defect in the wall of the cavity which measured 0.3 centimeter. On section, a collapsed cavity was found lined by smooth, glistening membrane. The microscopic diagnosis was "pericardial cyst."

Discussion

In the light of our case, it is interesting to consider the nature of the origin of true pericardial diverticulum. Lambert[5] clearly portrayed the nature of "thin-walled thoracic cysts," which he showed to be related to failure

of coalescence of the primitive lacunae of the pericardial anlage. Unequal development and partial coalescence result in diverticulum formation. As none of the cases cited (Mazer,[1] Cushing,[2] Haas,[3] Reitan,[4] and Abbott[6]) have been observed in early life, we must assume that pericardial diverticula exist either in a collapsed state or in similar nondetectable form, or as a congenital weakness of the pericardium (Haas[3]), and that in either instance there is added an incident factor of pericardial distention by fluid. Roesler[7] mentions increased intrapericardial pressure caused by hydropericardium, or by an enlarged heart, as a universal accompaniment. Other bodily abnormalities (such as inguinal hernia and colonic diverticulum) have comparable modes of origin.

The occurrence of an embryologic rest, which later in life secretes fluid and undergoes cyst formation, is well known; if this structure communicates with a normal absorptive surface, such as the pericardium, the fluid should never accumulate. Mechanical kinking of the isthmus with valve mechanism can result in distention of the diverticulum, the fluid being formed from its own membrane; or normal pericardial fluid may be squeezed into it by the massaging action of the heart beat.

Summary

A case of true diverticulum of the pericardium is reported, with a review of the literature. A cure was effected by excision of the cystic pericardial diverticulum.

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Studies of Tissue Response to Injections of Enzymes

I. The Development of Subcutaneous "Nodules" Following a Single Subcutaneous Injection of Trypsin

By SAMUEL THEODORE SCHLAMOWITZ, M.D., AND ARTHUR C. DEGRAFF, M.D.

Until recently, localized tissue trauma was considered the prime factor in the production of subcutaneous nodules in rheumatic subjects. The possibility that these lesions were "manifestations of the uninhibited action of proteinases on mesenchymal tissue" has its basis on the presence in human and animal sera of a proteolytic enzyme system similar to trypsin. The occurrence of subcutaneous "nodules" following a single subcutaneous injection of trypsin would seem to lend support to this thesis.

DREWITT[1] hypothesized that trauma, presumably mechanical, was involved in the production of subcutaneous nodules in patients with rheumatic fever. Attention was focused on this concept by the studies of Massell, Mote and Jones.[2] These investigators artificially induced subcutaneous nodules in patients with rheumatic fever by means of the combination of subcutaneous injection of the patient's own blood and localized pressure. It was the opinion of these authors that tissue injury of sufficient extent was of primary importance in the production of the subcutaneous nodule. Although cognizant that the inoculant per se may have some specific stimulating effect in the production of the nodules, they did not establish this fact.

A new concept regarding the production of subcutaneous nodules was introduced by Mirsky.[3] He successfully induced such nodules in rheumatic fever subjects by means of a single subcutaneous inoculation of crude or crystalline trypsin. He postulated that these lesions and other stigmata of rheumatic fever were a "manifestation of the uninhibited action of proteinases on mesenchymal tissue."

Mirsky's observations stimulated the present study, which was undertaken to ascertain whether a single subcutaneous injection of a proteolytic enzyme in rabbits would result in "nodule" formation at the injection site, and whether any visceral lesions might also develop.

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This Study was aided by grants from the American Legion and Helen Hay Whitney Foundation.

MATERIALS

This report is part of a study based on 122 young albino rabbits which received a single subcutaneous injection of a solution of one of the test substances, and which were subsequently examined macroscopically, microscopically[4] and chemically.[5]

Forty-four rabbits received crude or crystalline trypsin, 34 were untreated; the remaining 44 rabbits were divided into groups, the members of which received either saline, casein, crystalline bovine serum albumin, crystalline chymotrypsin, or crystalline lysozyme. The animals ranged in weight from 1.6 to 2.2 kilograms. They were purchased from Rockland Farms and maintained under standard laboratory conditions on Purina Chow. None of the animals in this series exhibited any clinical evidence of snuffles, ear canker, diarrhea, or cutaneous infection. The rabbits were examined daily. They were sacrificed by air embolism at specified intervals which varied from one to thirty days after the single subcutaneous inoculation. Postmortem examination was immediately performed, and various tissues and viscera, including the injection sites and hearts, were prepared for histologic[4] and chemical studies.[5]

METHODS

Measurement of the "Nodules." The plantar aspect of the hind legs, including the area of the "nodules," was shaved daily with a no. 2 Oster small-animal clippers. All measurements were performed daily with a vernier caliper graduated in millimeters. The "nodules" were measured along three perpendicular axes: a longitudinal, mediolateral, and dorsoplantar. The boundaries of the "nodules" were invariably so

sharply defined that there was no doubt where to apply the calipers.

Preparation of Solutions. Nine-tenths per cent sodium chloride with an initial pH 5.6 was adjusted to a pH 7.8 by the addition of 190 mg. disodium hydrogen phosphate ($Na_2HPO_4 \cdot 12H_2O$) per 100 milliliters. With this adjusted solvent the test substances were prepared as 1 per cent solutions. These solutions were brought to pH 7.4 by the addition of either dipotassium hydrogen phosphate (K_2HPO_4) or potassium dihydrogen phosphate (KH_2PO_4), as required. All solutions were sterilized by filtration through a Seitz filter, and completely utilized within one hour. The test substances employed in this study at a 1 per cent concentration were crystalline trypsin, crystalline chymotrypsin, crystalline lysozyme, crystalline bovine serum albumin, and casein. Crude trypsin solution was similarly prepared, except that a concentration of 4.2 per cent was employed instead of 1.0 per cent.

Enzyme Activity. Enzymatic activity of the trypsin and chymotrypsin preparation was determined by means of the Anson-Mirsky method.[6] It was found that the 1.0 per cent crystalline trypsin and 4.2 per cent crude trypsin solutions were of approximately equal enzymatic activity. Seitz filtration had no significant effect on the enzyme activity.

Procedure and Results

In a series of 13 rabbits, a single dose of 1.0 ml. of 4.2 per cent crude trypsin solution (containing 42 mg. of crude trypsin per ml.) was subcutaneously inoculated into a shaved area of the plantar surface of the hind legs, which is analogous to the human heel region. Following a lapse of four to seven days, there appeared at each of the injection sites a distinct, firm, nontender elevated mass (fig. 1), which progressively increased in size to reach its maximum in fourteen to eighteen days, and then slowly regressed. However, at the end of the thirty-day period, the firm, discrete, elevated mass was still present. There was never any erythema, tenderness, fluctuation, eschar, necrosis, slough, breakdown, or a fixation to the underlying tissue associated with the course of the development of the subcutaneous mass.

To ascertain whether the observations noted with the crude trypsin could be the result of a foreign protein reaction, or the irritative effect of the daily shaving, members of one group of 8 animals were subcutaneously given a single injection of 1 ml. of 1 per cent solution of pure casein, members of another group of 10 rabbits were subcutaneously inoculated with 1 ml. of 1 per cent crystalline bovine serum albumin solution,* and members of a third series of 34 animals were simply shaved daily for thirty days at the site where the other rabbits received the test substances. In both the casein and bovine serum albumin inoculated groups, following a short period (eighteen to twenty-four hours) of transitory edema, the injection sites appeared and remained normal throughout the experimental period. In the untreated group, the sites which were shaved daily exhibited no visible or palpable alteration from the normal (table 1).

To decide whether the previously described local lesions could be attributed to the enzymatic activity of the preparation, members of a group of 11 rabbits were subcutaneously inoculated with a single dose of 1 ml. of 4.2 per cent inactivated crude trypsin solution. Inactivation was accomplished by maintaining the solution in a water bath at 70° C. for two and a half hours. Although the enzymatic activity of the preparation was completely destroyed, as determined by the Anson-Mirsky method,[6] no physical change was visible in the solution. As was the case in the groups treated with casein and bovine serum albumin, and in the untreated groups, no visible or palpable alteration of the tissue occurred at the injection sites (table 1).

To determine whether the impurities in the crude trypsin preparation played any part in the production of the previously described lesions, members of a group of 12 rabbits were subcutaneously inoculated with 1 ml. of 1 per cent solution of twice-crystallized trypsin.† Such a solution actually contains only 5 mg. per ml. of enzyme, since 50 per cent of the twice-crystallized trypsin preparation is made up of magnesium sulfate. Members of another group of 8 rabbits were subcutaneously inoculated with a single injection of 1 ml. of 1 per cent heat-inactivated crystalline trypsin solution. Enzymatic inactivation of this crystalline

*This material was graciously donated by Dr. Max Schlamowitz, Department of Biochemistry, University of California, Berkeley, Calif.

†A portion of this material was graciously donated by Armour & Co., Chicago, Ill.

Table 1.—*Relationship between Occurrence, Size of "Nodules," and Time Interval after a Single Subcutaneous Inoculation of Test Substances*

Inoculant	Rabbit Number	Days Postinoculation													
		0.75	1	1.5	2	4	6	9	12	14	16	18	21	25	28
Crude trypsin	749	0													
	783	0	0												
	747	0	0												
	763	0	0	±											
	748	0	0	0	±										
	750	0	0	±	±	+									
	762	0	0	0	±	+	2+								
	685	0	0	±	±	+	2+								
	648	0	0	±	±	+	2+	2+	3+	4+	4+				
	730	0	0	0	±	+	+	2+	3+	4+	4+	4+			
	720	0	0	±	±	+	+	2+	3+	4+	4+	4+			
	679	0	0	±	±	+	+	2+	3+	4+	4+	4+	3+		
	693	0	0	+	+	+	+	2+	3+	4+	4+	4+	3+	2+	+
Crystalline trypsin	12	0	0												
	31	0	0	0	±										
	35	0	0	0	±										
	9	0	0	0	±	+									
	19	0	0	0	±	+	+								
	15	0	0	0	±	+	+								
	22	0	0	0	±	+	2+	3+							
	8	0	0	0	±	+	+	2+							
	13	0	0	0	+	+	2+	2+	3+						
	337	0	0	0	+	+	+	2+	3+	4+	4+				
	41	0	0	0	±	+	+	2+	3+	4+	4+	4+			
	48	0	0	0	+	+	+	2+	3+	4+	4+	4+	3+	2+	2+
1. Inactivated crystalline trypsin		0	0												
2. Crystalline bovine serum albumin		0	0												
		0	0	0	0										
3. Crystalline chymotrypsin		0	0	0	0	0									
4. Crystalline lysozyme		0	0	0	0	0	0								
5. Casein		0	0	0	0	0	0	0							
6. Saline		0	0	0	0	0	0	0	0	0					
		0	0	0	0	0	0	0	0	0	0	0			
		0	0	0	0	0	0	0	0	0	0	0	0	0	0

Key

Measurements (*mm.*)

Symbol	Length	x	Width	x	Height		Length	x	Width	x	Height
0	0		0		0	to	1		1		1
±	1		1		1	"	3		3		2
+	3		3		2	"	6		6		3
2+	6		6		2	"	8		8		4
3+	9		9		4	"	12		12		5
4+	12		12		5		or over*				

* Maximum nodule size observed 20 x 18 x 7.

trypsin preparation was accomplished by maintaining the solution at 70°C. for one and one half hours. No alteration of the physical appearance of the solution was noted. Following a lapse of four days there occurred, only in the group which received the active crystalline trypsin, tissue alteration of the type previously described (fig. 1, table 1) for the active crude trypsin.

It would seem that a causal relationship exists between the occurrence of the previously described firm, discrete subcutaneous masses (fig. 1) and the subcutaneous injection of either crude or crystalline trypsin. However, to verify this fact, further studies were required.

To learn what effect the introduction of saline buffered with phosphate to pH 5.00 might have, members of a group of 10 rabbits were subcutaneously inoculated with 1 ml. of this solution. As with the casein, bovine serum albumin, heat-inactivated crude trypsin and heat-inactivated crystalline trypsin, respectively, the injection sites did not exhibit any visible and/or palpable alteration from the normal (table 1).

In an attempt to answer the question as to whether the results obtained with crude and crystalline trypsin were specifically related to this proteolytic enzyme or could occur with other enzymes, members of a group of 8 rabbits were subcutaneously injected with 1 ml. of 1 per cent solution of crystalline chymotrypsin. This, like trypsin, is a proteolytic enzyme, pancreatic in origin. Members of another group of 8 rabbits were subcutaneously injected with 1 ml. of 1 per cent solution of lysozyme, a carbohydrase. The fact that neither chymotrypsin, the proteolytic enzyme, nor lysozyme, the carbohydrase, caused any visible or palpable tissue alteration at the injection sites during the experimental period would indicate that the occurrence of the subcutaneous "nodules" seems specifically related to trypsin.

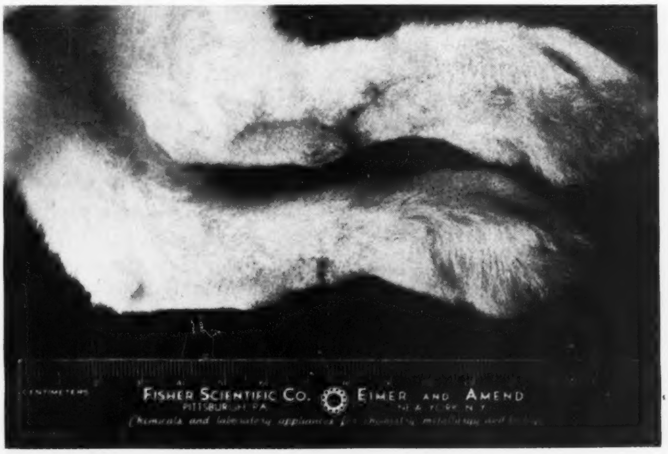

FIG. 1.—Subcutaneous "nodules" on the plantar aspect of the hind legs of Rabbit 720 which occurred at the site of injection of 1 ml. of 4.2 per cent crude trypsin. These "nodules" had, by the eighteenth postinoculation day, attained their maximum size.

DISCUSSION

The development of subcutaneous masses which were firm, discrete, nontender, nonfluctuant, not adherent to the underlying tissue, nor associated with necrosis, eschar, or erythema, in *only* those animals which were inoculated with active trypsin, crude or crystalline, focused our attention on several interesting facts.

The first and foremost of these facts concerns the role of mechanical trauma in the production of the subcutaneous masses. The

concept that mechanical tissue trauma plays a primary role in the production of subcutaneous nodules, as postulated by Drewitt,[1] and later by Massell, Mote, and Jones,[2] does not seem to be borne out in this study. This is suggested by the fact that those animals which did not develop "nodules," namely, those which received inactivated crude or crystalline trypsin, casein, crystalline bovine serum albumin, crystalline chymotrypsin, crystalline lysozyme, and saline pH 5.00, were for all practical purposes subjected to the same type and degree of mechanical trauma as were the rabbits which received the active proteolytic enzyme. The observed results emphasize the probability of a specific stimulating effect of trypsin. Although Massell, Mote and Jones[2] were fully cognizant of the possible stimulating effect of their inoculant (whole blood), they did not pursue this lead. In fact, the occurrence of subcutaneous "nodules" in a mesenchymal rich area, following the subcutaneous injection of only active crude and active crystalline trypsin, would seem to conform to Mirsky's[3] concept regarding the production of these lesions. Mirsky[3] was of the opinion that his studies supported the hypothesis that the lesions in rheumatic fever were the result of the "uninhibited action of proteinases on mesenchymal tissue." Although Mirsky's concept regarding the production of specific lesions was new, the basic fact upon which his concept is based, namely, the presence of serum and tissue proteolytic enzymes in man and animals, can be traced back to 1893 to the studies of Dastre.[7] Since then, the presence in human and animal sera of a proteolytic enzyme analogous to that of the pancreas has been repeatedly substantiated.[8-21]

However, the question as to whether enzymatic activity per se in a mesenchymal-rich area free of any mechanical trauma would result in "nodule" formation has yet to be determined. Such studies are now in progress.

The failure of subcutaneous "nodules" to arise at the sites of inoculation of the inactivated crude and crystalline trypsin, bovine serum albumin, casein, or at the sites shaved daily in the untreated group brings forth the fact that the occurrence of subcutaneous "nodules" seems primarily due to the enzymatic activity of the proteolytic enzyme, and not due to either a foreign protein reaction or the irritative effect of daily shaving.

The fact that subcutaneous "nodules" did not occur following the injection of chymotrypsin, which is also a pancreatic proteolytic enzyme, and lysozyme, which is a carbohydrase, seems to point to the specificity of trypsin.

Summary and Conclusion

1. A single subcutaneous inoculation of 1.0 ml. of 4.2 per cent solution of crude trypsin into the plantar surface of the hind legs of rabbits resulted after four to seven days in the occurrence of elevated, firm, discrete, nontender masses. There never was any erythema, tenderness, necrosis, slough, fluctuation, or breakdown associated with these masses.

2. Similar results were obtained with a single subcutaneous injection of 1 ml. of 1 per cent solution of active crystalline trypsin.

3. Subcutaneous injection of a single dose of either heat-inactivated crude or crystalline trypsin failed to produce any visible or palpable tissue alterations at the injection sites.

4. No visible or palpable alteration of the tissue at the injection sites occurred following the introduction of either buffered saline (pH 5.00), casein, or crystalline bovine serum albumin.

5. The subcutaneous injection of 1 ml. of 1 per cent solution of either crystalline chymotrypsin or crystalline lysozyme did not give rise to any visible or palpable alteration of the tissue from the normal at the injection sites.

6. From the results observed, it would seem that the occurrence of the subcutaneous masses are somehow specifically related to the enzymatic action of the proteolytic enzyme, trypsin.

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Studies of Tissue Response to Injections of Enzymes

II. Changes in Rabbit Plasma and Tissue Hexosamine Induced by a Single Subcutaneous Injection of Trypsin

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Hexosamine-containing polysaccharides have been demonstrated in plasma and various tissues including skin, cartilage and heart. Plasma hexosamine elevations have been observed in rheumatic fever, sterile infarcts and tuberculosis. It is possible that plasma polysaccharide changes reflect alterations of tissue polysaccharides. Thirty-six hours following a single subcutaneous injection of trypsin, a significant elevation of tissue hexosamine occurred at the injection sites. This appeared long before any visible or palpable change. The tissue hexosamine paralleled the developmental course of the "nodules." These findings appear specifically related to trypsin, since they failed to occur with other enzymes or test substances.

PLASMA and tissue hexosamine has been studied by a large number of investigators from several points of view. Their work has been recently reviewed by Meyer[1] and by Stacey.[2]

The combined studies of many of these investigators, [1-3] particularly those of Rimington,[4-7] Hewitt,[8] and Sorenson and Haugaard,[9] seem to indicate that the plasma polysaccharide consists of mannose, galactose, and glucosamine. The clinical significance of the study of the plasma polysaccharide becomes evident when one recalls that heparin, the blood group substances, and some antibodies contain glucosamine.[1, 2, 10] The demonstration of elevated plasma polysaccharide content in such conditions as pneumonia, tuberculosis, rheumatic fever, malignancy, and sterile infarcts[11-19] emphasizes the importance of the study of plasma polysaccharides.

Hexosamine-containing polysaccharides are not limited to the plasma, for they have been shown to be present in the cornea,[20] skin and cartilage,[10, 21] tendon, sclera, aorta, vitreous humor, synovial fluid, ciliary body, iris, and gastric mucosa.[10, 20-23]

That the alterations of plasma polysaccharides in disease may reflect alterations of the tissue polysaccharides is a possibility which is to be considered even though it is known that the tissue polysaccharides are different from the plasma polysaccharides. These polysaccharides differ from each other in the following ways: (a) tissue polysaccharides contain glucuronic acid, and either glucosamine or galactosamine, (b) plasma polysaccharides contain glucosamine, and neither galactosamine nor glucuronic acid, except for the glucuronic acid which comes from the relatively small amount of heparin present in the blood.

These facts together with the observation of visible tissue alterations following the single subcutaneous inoculation of the proteolytic enzyme, trypsin,[24] prompted this study. The present investigation was undertaken to ascertain the distribution of hexosamine in the various tissues of the normal rabbit and the alterations which occurred following the single subcutaneous injection of the proteolytic enzyme, trypsin, and the other test substances such as chymotrypsin, lysozyme, bovine serum albumin, casein, and saline (pH 5.0).

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Materials and Methods

The materials and animals which were employed in the preceding study[24] were also used for this work. Methods were as follows:

I. Determination of tissue hexosamine on wet-weight basis: Tissue hexosamine was determined by a modification of the method developed by Schloss[25] for the determination of plasma hexosamine and was carried out as follows:

(*a*) Approximately 500 mg. of each of the various tissues which were excised from each animal (table 1) were weighed.

(*b*) Assuming that water comprises 80 per cent of the tissue weight, sufficient distilled water (approximately 0.6 ml.) was added to make up a total volume of 1.0 ml. of water, and then 1.0 ml. of 8 N (normal) hydrochloric acid was added.

(*c*) The tubes were sealed and placed in a boiling water bath for six hours.

(*d*) The contents of the tubes were quantitatively transferred to a 50-ml. Folin-Wu tube, and made up to volume with distilled water.

(*e*) Seventy-five one-hundredths milliliter of Darco (activated carbon), as measured in a hematocrit tube, was added to the solution. The mixture was thoroughly and vigorously shaken for five minutes to distribute the carbon particles equally throughout the solution.

(*f*) The solution was then filtered through No. 40 Whatman paper.

(*g*) The procedure from this point forth is identical with that described by Schloss.[25]

II. Determination of tissue hexosamine on dry-weight basis:

(*a*) This was carried out simultaneously with the wet-weight determination on a separate sample first weighed wet and again weighed after drying in an oven at 100 C. for twenty-four to twenty-six hours.

(*b*) The dried tissue was treated in the same manner as the wet tissue (Part I, *b* to *g*). All skin samples must be shaved as closely as possible because fur, per se, gives rise to a color which interferes with the hexosamine determination.

III. The plasma hexosamine and the hexosamine content of the test substances were determined by the method described by Schloss.[25]

IV. Statistical analysis: The standard deviation was determined by means of the formula $\sigma = \sqrt{\frac{\Sigma f d^2}{n}}$ when the number of animals studied was 30 or more and by the formula $\sigma = \sqrt{\frac{\Sigma f d^2}{n-1}}$ when the number of animals studied was less than 30. The test of significance or "*t*" test was done to determine whether variations from the control were significant. The value of "*t*" was determined by the equation $t = \sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}}$; "*t*" values of 2.50 or over were considered as significant.

In the preceding formulas, σ = standard deviation; Σ = sum of; f = frequencies; d = deviation from the mean; n = number of observations; and m = mean.

Results

Tissues of normal or untreated rabbits can be divided into three classes depending upon their hexosamine content. Table 1 summarizes the analytic results of various tissues of untreated rabbits. Class I consists of such tissues as the heart, thymus, testes, and quadriceps femoralis, which are poor in collagen, fibrous connective tissue, and ground substances and which exhibit a relatively low hexosamine content. Tendon, lung, kidney, stomach, and the osseous portion of ribs (table 1, Class III) exhibit a relatively high hexosamine value. With the exception of the stomach and ribs, the relatively high hexosamine content of the remaining tissues of this class is most probably due to the fact that these tissues are relatively rich in collagen, ground substance, or fibrous connective tissue. The high hexosamine values of the stomach are due to the presence of the hexosamine-containing polysaccharide, mucoitin sulfate, in the mucosa. The high hexosamine content of the rib is due to the hexosamine-containing polysaccharide, chondroitin sulfate. Tissues such as liver, spleen, and tongue comprise the third class, containing an intermediate amount of hexosamine (table 1, Class II).

The range and mean value of the plasma

TABLE I.—*Comparison of the Mean Hexosamine Content of the Various Tissues in Untreated Rabbits and in Those Which Received a Single Subcutaneous Injection of the Various Test Substances**

Inoculant	No. of Animals Examined	Range	Mean	σ	t
		Class I			
		Striated Muscle (Quadriceps Femoralis)			
Untreated	34	0.23–0.50	0.35	±0.09	—
Crude trypsin	7	0.33–0.49	0.40	±0.07	1.51
Inactivated crude trypsin	11	0.29–0.47	0.31	±0.04	1.81
Casein	8	0.30–0.45	0.39	±0.06	1.43
Saline	8	0.31–0.37	0.33	±0.02	1.00
		Heart			
Untreated	34	0.34–0.68	0.54	±0.12	—
Crude trypsin	7	0.36–0.61	0.53	±0.10	0.22
Inactivated crude trypsin	11	0.40–0.51	0.49	±0.04	2.08
Casein	8	0.43–0.60	0.50	±0.06	1.33
Saline	8	0.39–0.58	0.51	±0.06	1.00
		Thymus			
Untreated	34	0.43–0.71	0.58	±0.09	—
Crude trypsin	7	0.40–0.78	0.65	±0.10	1.67
Inactivated crude trypsin	11	0.42–0.67	0.54	±0.08	1.43
Casein	8	0.46–0.72	0.62	±0.09	1.08
Saline	8	0.49–0.63	0.56	±0.04	1.00
		Testis			
Untreated	20	0.61–0.82	0.70	±0.05	—
Crude trypsin	7	0.57–0.77	0.67	±0.10	0.72
Inactivated crude trypsin	9	0.55–0.80	0.63	±0.08	2.33
Casein	8	0.58–0.77	0.69	±0.05	0.45
Saline	6	0.61–0.77	0.69	±0.05	0.40
		Class II			
		Liver			
Untreated	34	0.85–1.25	0.96	±0.12	—
Crude trypsin	7	0.86–1.10	0.92	±0.05	1.40
Inactivated crude trypsin	8	0.88–0.98	0.91	±0.05	1.78
Casein	8	0.88–1.12	0.96	±0.27	0.00
Saline	8	0.76–1.01	0.89	±0.10	1.55
		Tongue			
Untreated	30	0.67–1.13	0.89	±0.15	—
Crude trypsin	7	0.84–1.09	0.92	±0.08	0.74
Inactivated crude trypsin	10	0.69–0.82	0.80	±0.06	2.02
Casein	8	0.89–1.14	0.96	±0.12	1.32
Saline	7	0.63–0.94	0.78	±0.14	1.72
		Spleen			
Untreated	30	0.72–1.05	0.90	±0.12	—
Crude trypsin	7	0.80–1.10	0.99	±0.12	1.66
Inactivated crude trypsin	9	0.73–1.00	0.84	±0.07	1.80
Casein	8	0.90–1.07	0.96	±0.04	2.30
Saline	7	0.81–1.27	0.96	±0.15	0.90

TABLE 1.—*Continued*

Inoculant	No. of Animals Examined	Range	Mean	σ	t
Class III—Skin†					
Untreated	34	1.00–1.56	1.24	±0.15	—
Crude trypsin	12	1.05–1.52	1.27	±0.15	0.54
Inactivated crude trypsin	12	0.92–1.45	1.23	±0.26	0.12
Casein	8	0.92–1.48	1.17	±0.20	0.88
Saline	10	1.00–1.55	1.18	±0.14	1.11
Crystalline bovine serum albumin	10	1.05–1.56	1.31	±0.17	1.13
Crystalline trypsin	12	0.90–1.60	1.34	±0.17	1.91
Inactivated crystalline trypsin	9	1.18–1.70	1.36	±0.22	1.48
Crystalline chymotrypsin	8	1.08–1.52	1.30	±0.13	1.07
Crystalline lysozyme	7	1.03–1.61	1.36	±0.21	1.34
Tendon‡					
Untreated	31	1.12–1.72	1.36	±0.18	—
Crude trypsin	12	1.00–1.60	1.28	±0.17	1.29
Inactivated crude trypsin	12	1.11–1.43	1.25	±0.11	2.29
Casein	8	1.10–1.33	1.26	±0.08	2.22
Saline	10	1.28–1.64	1.40	±0.11	0.83
Crystalline bovine serum albumin	10	1.12–1.74	1.42	±0.13	1.11
Crystalline trypsin	12	1.10–1.70	1.42	±0.20	1.18
Inactivated crystalline trypsin	9	1.00–1.75	1.53	±0.26	1.75
Crystalline chymotrypsin	8	1.06–1.76	1.41	±0.22	0.56
Crystalline lysozyme	7	0.98–1.64	1.29	±0.27	0.60
Lung					
Untreated	24	0.89–1.42	1.19	±0.14	—
Crude trypsin	7	1.00–1.30	1.19	±0.07	0.00
Inactivated crude trypsin	9	0.89–1.45	1.10	±0.15	1.47
Casein	8	1.01–1.50	1.30	±0.19	1.42
Saline	8	0.99–1.57	1.26	±0.16	1.01
Kidney					
Untreated	20	1.00–1.54	1.27	±0.17	—
Crude trypsin	7	0.99–1.20	1.16	±0.07	2.28
Inactivated crude trypsin	9	0.98–1.40	1.11	±0.18	2.13
Casein	8	0.98–1.30	1.14	±0.10	2.40
Saline	7	1.03–1.37	1.13	±0.11	2.37
Rib					
Untreated	26	0.95–1.60	1.30	±0.25	—
Crude trypsin	7	0.91–1.40	1.22	±0.17	0.90
Casein	8	0.99–1.45	1.19	±0.05	2.09
Saline	9	0.90–1.41	1.15	±0.16	2.00
Stomach					
Untreated	26	1.29–2.50	1.58	±0.40	—
Crude trypsin	7	1.20–2.50	1.74	±0.44	0.80
Inactivated crude trypsin	9	1.13–1.74	1.36	±0.21	2.02
Casein	8	1.14–1.75	1.42	±0.22	1.39
Saline	9	1.30–1.66	1.49	±0.13	0.98
Class IV—Plasma Hexosamine (mg. per 100 ml. plasma)					
Untreated	34	39.1–67.0	51.4	±6.80	—

* All values are expressed in milligrams hexosamine per gram of wet tissue and cover the entire experimental period. † Skin covering the quadriceps femoralis—a site distant from injection site. ‡ Tendon of Achilles—underlying the injection site.

TABLE 2.—*Comparison of the Mean Hexosamine Content of the Injection Sites and "Nodules" Following a Single Subcutaneous Injection of the Various Test Substances**

Inoculant	No. of Animals Examined	Range	Mean	σ	t
Untreated	26	4.02–6.10	5.16	±0.66	–
Crude trypsin	11	6.30–12.10	7.31	±1.73	3.83
Inactivated crude trypsin	12	4.54– 5.98	5.58	±0.62	1.83
Casein	9	3.59– 6.00	4.72	±0.92	0.46
Saline	10	4.45– 5.75	5.13	±0.51	0.13
Crystalline bovine serum albumin	11	4.00– 6.09	5.60	±0.77	1.54
Crystalline trypsin	12	6.00– 8.90	7.47	±0.85	8.02
Inactivated crystalline trypsin	10	4.87– 5.76	5.34	±0.24	1.12
Crystalline chymotrypsin	8	4.44– 5.56	4.94	±0.40	1.10
Crystalline lysozyme	7	3.41– 5.98	4.90	±0.58	0.96

* All values are expressed as milligrams hexosamine per gram of dried tissue, and cover the entire experimental period.

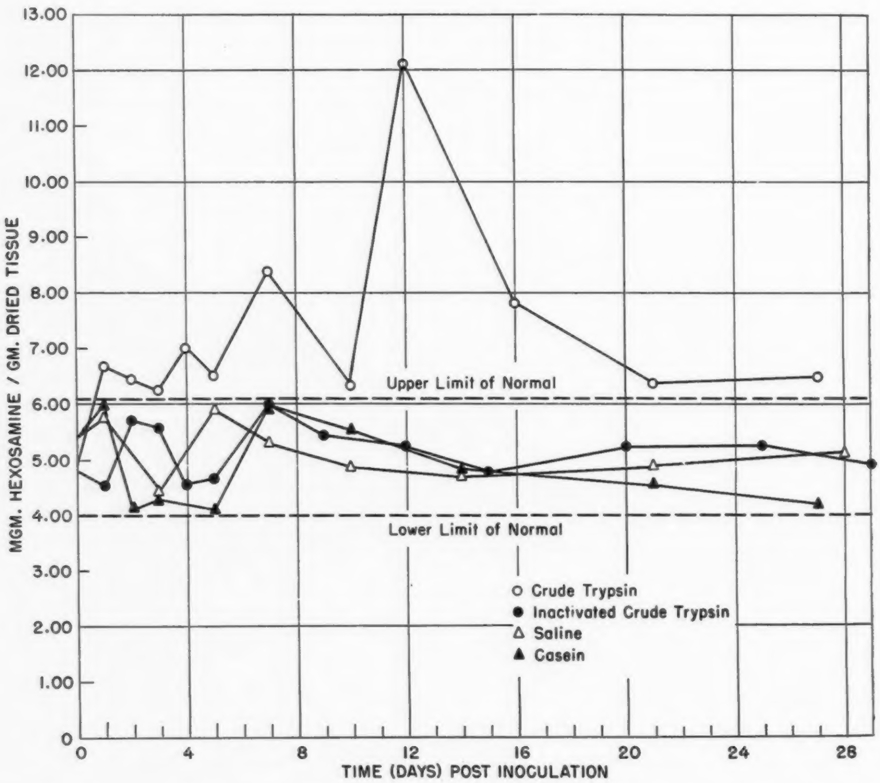

FIG. 1.—Comparison of tissue hexosamine changes following a single subcutaneous injection of crude trypsin, inactivated crude trypsin, casein and saline.

hexosamine content of the untreated group of rabbits is exhibited in table 1, Class IV.

Following a single subcutaneous injection of crude or crystalline trypsin, there were no visible or palpable tissue changes at the injection site for four to seven days.[24] Although before any visible or palpable change was noted. Following the initial rise, the hexosamine content of the tissues and "nodules" at the injection sites remained significantly elevated throughout the experimental period. The secondary rise in the already elevated hexos-

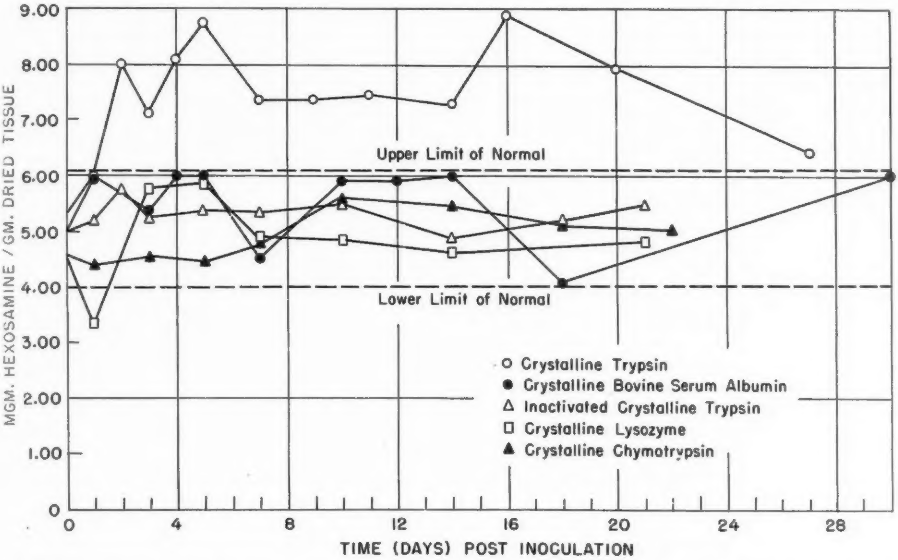

FIG. 2.—Comparison of tissue hexosamine changes following a single subcutaneous injection of crystalline trypsin, inactivated crystalline trypsin, crystalline bovine serum albumin, crystalline lysozyme and crystalline chymotrypsin.

no physical changes were noted at the injection sites during this period, the possibility that measurable changes in hexosamine content had occurred was considered. Therefore, hexosamine determinations were performed on the various tissues, including the injection sites, and plasma (tables 1 and 2).

It is seen in figures 1 and 2 and table 2 that a significant increase in hexosamine concentration at the injection sites and "nodules" followed a single subcutaneous injection of crystalline trypsin. Inactive crude and crystalline trypsin as well as the other test substances did not cause any significant change in hexosamine concentration locally. Of interest is the marked increase in the hexosamine content of the tissue at the injection sites, which occurred as early as thirty-six hours postinoculation (figs. 1 and 2). This alteration occurred long

TABLE 3.—*Hexosamine Content of the Various Test Substances**

Test Substances	Hexosamine Content
4.2% crude trypsin solution	0.007
1.0% crystalline trypsin solution	0.003
1.0% casein solution	0.007
1.0% crystalline bovine serum albumin solution	0.005
1.0% crystalline lysozyme solution	0.005
1.0% crystalline chymotrypsin solution	0.003

* Expressed as milligrams of hexosamine per milliliter of solution of the test substances, which is the exact amount of hexosamine introduced via the injection.

amine content (figs. 1 and 2) which occurred between the fourteenth and eighteenth day after inoculation corresponded to the period when the "nodule" reached its maximum size.

At the end of the experimental period, thirty days postinoculation, the hexosamine value at the site of injection was still elevated (figs. 1 and 2) and the "nodule" although small in size was still present. The fact that similar results were obtained with both crude and crystalline trypsin demonstrates that the impurities in the crude preparation played no

TABLE 4.—*Comparison of Mean Hexosamine Content of the Skin* and Tendon† Following a Single Subcutaneous Injection of the Various Test Substances‡*

Inoculant	No. of Animals Examined	Range	Mean	σ	t
Skin*					
Untreated	26	2.03–5.90	4.14	±1.04	—
Crude trypsin	10	2.24–5.40	4.31	±0.92	0.56
Inactivated crude trypsin	12	2.97–4.70	3.77	±0.39	1.81
Casein	9	2.10–5.88	4.73	±1.09	1.35
Saline	8	3.06–5.23	4.42	±0.73	0.81
Crystalline bovine serum albumin	10	3.09–5.30	4.49	±0.40	1.48
Crystalline trypsin	12	3.46–5.00	4.56	±0.57	1.19
Inactivated crystalline trypsin	9	3.72–5.90	4.53	±0.65	1.28
Crystalline chymotrypsin	8	3.56–5.38	4.22	±0.62	0.29
Crystalline lysozyme	7	3.40–5.52	4.35	±0.76	0.60
Tendon†					
Untreated	26	2.65–5.10	4.13	±0.76	—
Crude trypsin	10	2.82–5.66	4.45	±0.90	0.94
Inactivated crude trypsin	12	3.30–5.20	3.94	±0.63	0.79
Casein	9	3.00–5.60	4.42	±0.87	0.85
Saline	8	3.52–5.63	4.40	±0.66	0.79
Crystalline bovine serum albumin	10	3.20–5.10	4.25	±0.65	0.43
Crystalline trypsin	12	4.00–5.40	4.41	±0.56	1.23
Inactivated crystalline trypsin	9	3.80–5.18	4.50	±0.51	1.57
Crystalline chymotrypsin	8	4.02–5.44	4.27	±0.57	0.29
Crystalline lysozyme	7	3.92–4.92	4.06	±0.66	0.23

* Skin covering the quadriceps femoralis—a site distant from the injection site.
† Tendon of Achilles—subjacent to the injection site.
‡ All values are expressed as milligrams of hexosamine per gram of dried tissue, and cover the entire experimental period.

TABLE 5.—*Comparison of the Mean Plasma Hexosamine Content of the Untreated Rabbits and of Those Which Received a Single Subcutaneous Injection of the Various Test Substances**

Inoculant	Examined	Range	Mean	σ	t
Untreated	30	39.1–67.0	51.4	±6.80	—
Crude trypsin	12	49.5–87.0	77.5	±12.80	4.73
Inactivated crude trypsin	12	30.0–69.6	53.5	±10.60	0.64
Casein	9	45.5–70.3	59.9	±8.40	2.63
Saline	8	39.0–82.1	58.7	±13.51	1.53
Crystalline trypsin	10	55.5–77.4	67.9	±7.53	6.39
Inactivated crystalline trypsin	10	40.0–72.0	53.9	±3.22	1.52
Crystalline bovine serum albumin	10	70.0–96.0	79.3	±9.21	8.23
Crystalline chymotrypsin	8	46.0–90.6	73.0	±14.90	3.74
Crystalline lysozyme	7	45.6–89.1	74.9	±15.74	3.59

* All values are expressed as milligrams hexosamine per 100 milliliters of plasma and cover the entire experimental period.

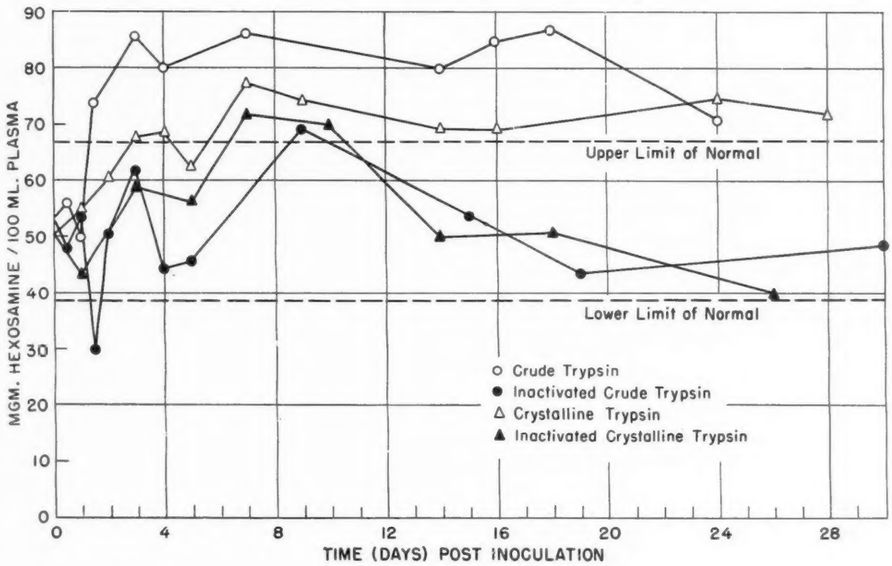

FIG. 3.—Comparison of plasma hexosamine values in rabbits following a single subcutaneous injection of crude trypsin, crystalline trypsin, inactivated crude and crystalline trypsin.

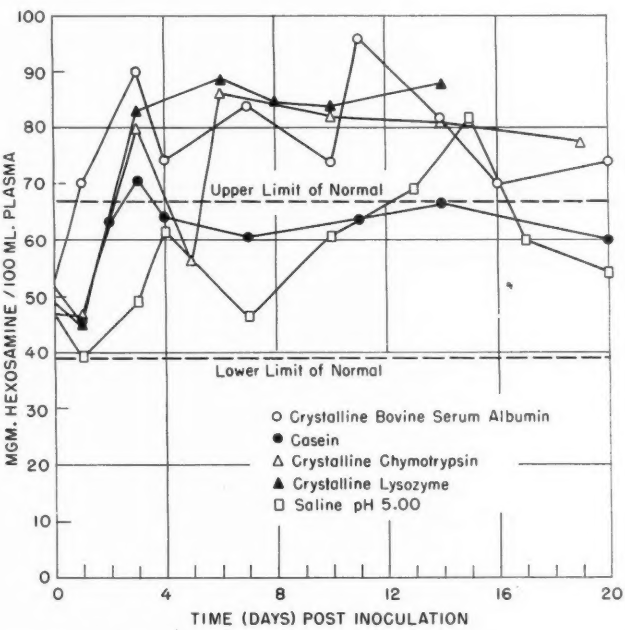

FIG. 4.—Comparison of plasma hexosamine values in rabbits following a single subcutaneous injection of saline, casein, crystalline lysozyme, crystalline chymotrypsin, and crystalline serum albumin.

important part in the formation of the "nodules."

The hexosamine content of the various test substances is listed in table 3. The insignificant amount of hexosamine present in the test substances, introduced via the injection, could hardly account for the elevated values obtained at the injection sites and "nodules."

Although the "nodules" and injection sites exhibited significantly elevated hexosamine values following the subcutaneous injection of crude and crystalline trypsin (table 2, figs. 1 and 2), the other tissues failed to demonstrate any significant alteration of the hexosamine content from the normal (table 4).

In table 5 and figure 3 it is seen that the plasma hexosamine value for the group of rabbits inoculated with crude trypsin was significantly elevated as early as forty-eight hours postinoculation and remained so throughout this experimental period. By the third postinoculation day, the plasma hexosamine value of the crystalline trypsin group rose significantly and remained elevated throughout the study period.

It was determined that the "nodules" which occurred following the single subcutaneous injection of crude or crystalline trypsin were due neither to a foreign protein reaction nor to a nonspecific reaction to the injection per se, nor to the irritative effect of daily shaving, nor could they be produced by other enzymes.[24] Concomitant with the absence of any macroscopic tissue changes following the single subcutaneous injection of casein, crystalline bovine serum albumin, saline, crystalline lysozyme, crystalline chymotrypsin, and daily shaving was the failure of any significant hexosamine changes to occur either at the injection sites (table 2) or in the other tissues (tables 1 and 4).

The significant elevation of the plasma hexosamine above the upper normal limit which occurred following the subcutaneous inoculation of crystalline bovine serum albumin, crystalline chymotrypsin, crystalline lysozyme, and casein (fig. 4) is something which deserves further investigation.

Discussion

The present studies not only confirm the presence of an hexosamine in such rabbit tissues as skin, tendon, cartilage, and gastric mucosa[20-23] (table 1), but have also demonstrated its presence in a large variety of other tissues (table 1). A direct relationship seems to exist between the hexosamine content and amount of collagen and/or fibrous connective tissue present (table 1).

Since subcutaneous "nodules" appeared only in those rabbits treated with trypsin and since these "nodules" were preceded by and associated with a significantly elevated tissue hexosamine content at the injection sites (table 2, figs. 1 and 2), it is possible that histochemical alterations are earlier indices of pathologic changes than are macroscopic observations. It is conceivable that tissue hexosamine alteration may be employed as a means for the earlier detection of the presence of pathologic processes.

Statistically significant elevations of the hexosamine values of the injection sites and "nodules" which followed occurred only in those rabbits inoculated with active crude and crystalline trypsin (table 2).

The occurrence of significantly elevated plasma hexosamine values in those animals inoculated with substances which caused no histochemical or macroscopic changes at the injection site (casein, albumin, chymotrypsin, and lysozyme), as well as in those rabbits inoculated with other substances (crude and crystalline trypsin) which caused macroscopic and significant histochemical changes, indicates that there is probably no direct relationship between the plasma and tissue hexosamine changes.

Summary and Conclusions

1. Following a single subcutaneous injection of 1.0 ml. of a crude or crystalline trypsin solution into the plantar aspect of the hind legs of rabbits, there occurred a significant elevation of the hexosamine content of the tissue at the injection site. The "nodules" which subsequently developed had without exception

the highest hexosamine content of all the tissues studied.

2. The elevation of the tissue hexosamine of the injection sites occurred before any visible or palpable tissue changes could be detected, and persisted throughout the experimental period of thirty days.

3. That the results obtained with trypsin were specifically due to its enzymatic action was indicated by the failure of any significant alteration of tissue hexosamine or macroscopic changes to occur following the subcutaneous injection of casein, crystalline bovine serum albumin, heat-inactivated trypsin, crystalline chymotrypsin, and crystalline lysozyme.

4. The tissue hexosamine content of such tissues as the skin, tendon, lung, heart, liver, spleen, and thymus did not exhibit any significant alteration following the subcutaneous injection of the test substances including trypsin.

5. The plasma hexosamine was significantly elevated, as demonstrated by the *t* test, in members of the groups which received active crude or crystalline trypsin, chymotrypsin, lysozyme, bovine serum albumin, and casein. It was not significantly elevated in members of the inactivated trypsin and saline groups.

6. The occurrence of a significantly elevated plasma hexosamine value in those groups whose members did not exhibit any significant tissue hexosamine changes illustrates the lack of any necessary correlation between the tissue and plasma hexosamine changes following the subcutaneous introduction of the test substances.

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Studies of Tissue Response to Injections of Enzymes

III. Preliminary Report. Development of Subcutaneous "Nodules" and Tissue Hexosamine Changes in Rabbits Following a Single Subcutaneous Injection of Streptokinase

By Samuel T. Schlamowitz, M.D., Arthur C. DeGraff, M.D., and Maxwell Schubert, Ph.D.

Since 1893, activation of the serum proteolytic enzymes has been accomplished by a variety of methods and agents. Activation of the serum proteolytic enzyme by means of streptokinase, the beta hemolytic streptococcal kinase, has been recently demonstrated. The significant plasma and tissue hexosamine changes, as well as the subcutaneous "nodules" which developed at the injection sites, resemble those observed in the trypsin treated group. Although trypsin and the serum proteolytic enzyme are not identical, they have many characteristics in common.

THE PRESENCE of proteolytic activity of serum was first noted by Dastre[1] in 1893. Delezene and Pozerski[2] in 1903 reported that sera treated with chloroform exhibited proteolytic activity. This observation has been confirmed by subsequent investigators.[3-6] Activation of serum protease has been accomplished by a variety of agents and methods.[7-10] Christensen[11] and Christensen and MacLeod[5] have recently demonstrated that serum protease is normally present as a zymogen, plasminogen,[5] and is catalytically transformed to an active enzyme, plasmin, by streptokinase, a bacterial kinase. Despite the fact that plasmin and trypsin have many characteristics in common and are considered to be identical by some investigators,[13-16] Christensen[5, 11] and Kaplan[12] have demonstrated that they are not identical.

This study was prompted by the following considerations: (1) the development of subcutaneous "nodules" in rabbits appeared to be specifically related to the administration of trypsin;[17] (2) the fact that plasmin and trypsin have many characteristics in common;[12] and (3) the fact that plasminogen is converted to plasmin by streptokinase.[11] It was decided to ascertain whether a single subcutaneous injection of streptokinase would induce (a) "nodule" formation at the injection site, other local lesions, and/or visceral lesions; (b) any significant changes in tissue and/or plasma hexosamine.[18]

Materials and Methods

Seven young male albino rabbits* were used in this study. These animals ranged in weight from 1.60 to 1.92 kilograms. They were obtained from the same source and fulfilled the same criteria regarding their clinical state as those employed in the previous studies.[17, 18] Except for the inoculant, these rabbits were subjected to the same procedures employed in the previous investigation.[17, 18]

The control animals employed for this study are the same as those used in the previous studies.[17, 18]

Streptokinase.† Partially purified streptokinase made up in a borate buffered solution (pH 7.4) was prepared so that 1.0 ml. of the solution contained 10,000 units.

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This Study was aided by grants from the American Legion and Helen Hay Whitney Foundation.

* The limited amount of streptokinase available was sufficient for only 7 animals.

† Partially purified streptokinase was graciously contributed by Drs. C. MacLeod and L. R. Christensen, Department of Microbiology, New York University College of Medicine.

TABLE 1.—*The Relationship Between the Occurrence, Size of the "Nodules," and the Time Interval After a Single Subcutaneous Inoculation of Streptokinase*

Key—Measurements in mm.

Symbol	Length × Width × Height				Length × Width × Height		
0	0	0	0	to	1	1	1
±	1	1	1	"	3	3	2
+	3	3	2	"	6	6	3
2+	6	6	3	"	9	9	4
3+	9	9	4	"	12	12	4
4+	12	12	12	"	or over*		

* Maximum nodules since observed 22 × 22 × 10.

Inoculant	Rabbit Number	Days Postinoculation 1	2	3	5	7	9	12	14	16	18	21
Streptokinase	30	0										
	38	0	+	4+								
	32	0	±	3+	3+							
	42	0	+	3+	3+	4+						
	45	0	±	2+	2+	3+	4+					
	40	0	±	2+	2+	3+	4+	4+	4+			
	36	0	±	2+	3+	3+	4+	4+	4+	4+	4+	3+

The methods for the measurement of the "nodules," the determination of the hexosamine content of the plasma and tissues, and the statistical treatment of the results which were employed in this study have been described in detail in the previous reports.[17, 18]

PROCEDURE AND RESULTS

In each of a series of 7 rabbits, a single injection of 1.0 ml. of streptokinase solution containing 10,000 units was introduced subcutaneously into the shaved area of the plantar surface of each of the hind legs, which is analogous to the human heel region. A distinct, firm, nontender, elevated mass appeared at the injection site two to four days after the injection. The subcutaneous "nodule" progressively increased in size to reach its maximum in nine to sixteen days, and then slowly regressed (table 1, fig. 1). At the end of the experimental period of twenty-one days, the "nodule" although smaller in size, was still present. No erythema, tenderness, fluctuation, eschar, necrosis, slough, breakdown, or fixation to the underlying tissue was associated with the developmental course of the subcutaneous mass.

Twenty-four hours after the single subcutaneous injection of 10,000 units (1.0 ml.) of streptokinase, a significant elevation of the tissue hexosamine content occurred at the injection sites. Thereafter the level of the hexosaamine of the injection sites and "nodules" remained significantly elevated throughout the experimental period of twenty-one days (fig. 1, table 2).

The hexosamine content of such tissues as the tendons of Achilles, and the skin covering

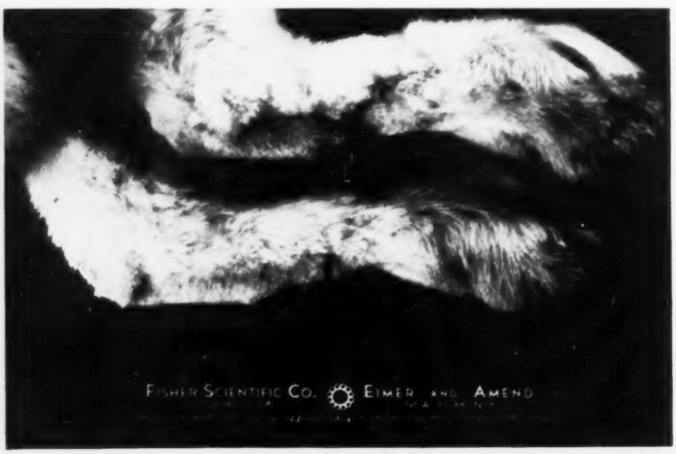

FIG. 1.—Streptokinase "nodules" on the plantar surface of the hind legs of Rabbit 36, which occurred at the injection sites twelve days after the subcutaneous injection of 10,000 units of streptokinase.

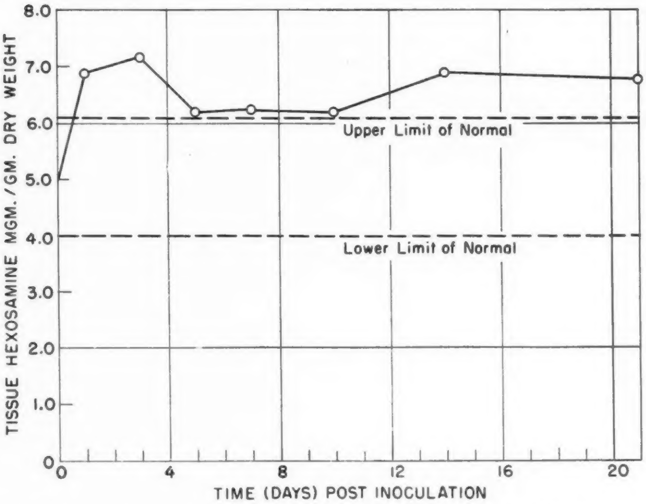

FIG. 2.—Tissue hexosamine changes of the injection sites and "nodules" following a single subcutaneous injection of streptokinase.

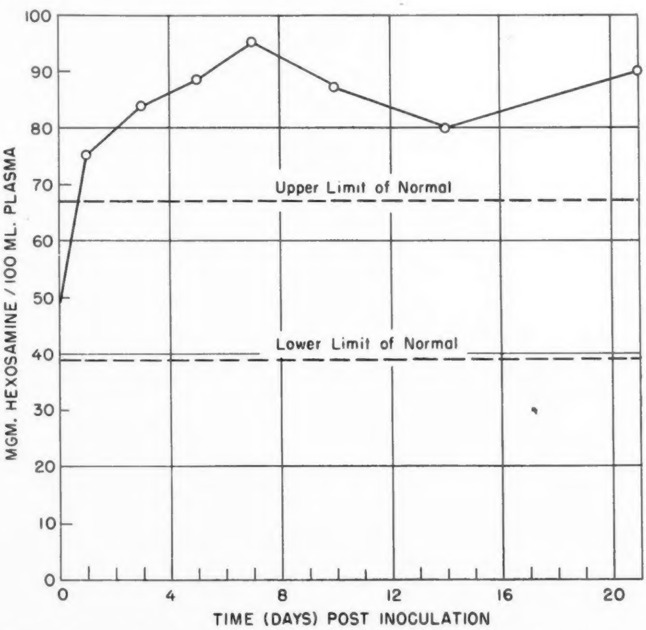

FIG. 3.—Plasma hexosamine changes following a single subcutaneous injection of streptokinase.

the quadriceps femoralis (a site distant from the injection area), did not exhibit any significant variation from the normal (table 3).

A significant elevation of the plasma hexosamine occurred twenty-four hours after the single subcutaneous injection of streptokinase and persisted throughout the entire twenty-one-day study period (fig. 2, table 4).

Discussion

Subcutaneous "nodules" which macroscopically resembled those which followed the single

TABLE 2.—*Comparison of the Mean Hexosamine Content of the Injection Sites and "Nodules" Following a Single Subcutaneous Injection of Streptokinase**

Inoculant	Number of Animals Examined	Range	Mean	σ	t
Untreated.....	27	4.02–6.10	5.16	±0.66	—
Streptokinase..	7	6.10–7.20	6.63	±0.39	7.24

* All values are expressed as milligrams of hexosamine per gram of dry tissue, and cover the entire experimental period.

TABLE 3.—*Comparison of the Mean Hexosamine Content of the Tendons,* and Skin† Following a Single Subcutaneous Injection of Streptokinase*

All values are expressed as milligrams of hexosamine per gram of dry tissue, and cover the experimental period.

† Skin Over the Quadriceps Femoralis

Inoculant	Number of Animals Examined	Range	Mean	σ	t
Untreated.....	27	2.03–5.90	4.14	±1.04	—
Streptokinase..	7	3.90–5.12	4.33	±0.47	0.64

* Tendons of Achilles

Inoculant	Number of Animals Examined	Range	Mean	σ	t
Untreated.....	27	2.65–5.10	4.13	±0.76	—
Streptokinase..	7	3.35–4.98	4.15	±0.57	0.07

TABLE 4.—*Comparison of the Mean Plasma Hexosamine Content of Untreated and Streptokinase Treated Rabbits**

Inoculant	Number of Animals Examined	Range	Mean	σ	t
Untreated.....	30	39.1–67.0	51.4	±6.80	—
Streptokinase..	7	75.0–95.4	85.4	±6.70	11.3

* All values are expressed as milligrams hexosamine per 100 ml. of plasma and cover the entire experimental period.

subcutaneous injection of crude or crystalline trypsin[17] developed locally at the sites where the partially purified streptokinase was injected. The developmental course of these "nodules" seemed to be accelerated when compared with that which occurred in the animals inoculated with trypsin. This is demonstrated by the fact that in the streptokinase-treated series, "nodules" appeared in two to four days after injection and reached their maximum size within twelve to sixteen days. In the trypsin-treated series, the "nodules" appeared within four to eight days, and reached their maximum in fourteen to eighteen days.[17]

The significant elevation of the tissue (injection sites and "nodules") and plasma hexosamine content which occurred soon after the introduction of streptokinase and persisted throughout the period of observation resembled the hexosamine changes observed in the trypsin-treated rabbits.[18] Another feature common to both the streptokinase-inoculated rabbits and trypsin-injected animals is the secondary rise in the hexosamine content of the "nodules" twelve to eighteen days after inoculation (fig. 1) which corresponds to the period when the "nodules" reached their maximum size.

The inoculating dose of streptokinase was assumed to produce sufficient plasmin not only to neutralize the high antiprotease titer which is present in the rabbit,[6, 19] but also to insure an excess of the plasmin. The hypothesis that the "nodule" formation and hexosamine changes observed following the injection of streptokinase were due to the plasmin resulting from the activation of the plasminogen by the streptokinase[5, 11] can hardly be made at present. The possible role of desoxyribosenuclease which has been demonstrated to be present in the partially purified streptokinase preparations[20] must first be investigated.

SUMMARY

1. Two to four days following a single subcutaneous injection of 10,000 units of partially purified streptokinase into the plantar aspect of the hind legs of rabbits, there occurred at the injection site a distinct, firm, nontender, elevated mass. There never was any erythema, tenderness, eschar, necrosis, slough, breakdown, fluctuation, or fixation to the underlying

tissues associated with the development of the "nodules."

2. The "nodules" progressively increased in size to reach their maximum in twelve to sixteen days postinoculation, and then slowly regressed.

3. The injection sites and the "nodules" which subsequently developed exhibited a significant increase in the hexosamine content, which persisted throughout the twenty-one days of observation.

4. A significant increase in the plasma hexosamine content occurred twenty-four hours after the inoculation, and persisted throughout the entire study period.

ACKNOWLEDGMENT

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Studies of Tissue Response to Injections of Enzymes

IV. Tissue, Hexosamine, and Hematologic Changes in Rabbits Following a Single Subcutaneous Injection of Hyaluronidase

By Samuel T. Schlamowitz, M.D., Evelyn Morrison, A.B., and Maxwell Schubert, Ph.D.

Hyaluronic acid, a mucopolysaccharide, is present in a variety of tissues, including the skin, vitreous humor, and synovial fluid. It is depolymerized and hydrolyzed by hyaluronidase, with the liberation of a hexosamine and glucuronic acid. A significant elevation of tissue hexosamine occurred at the injection sites and in the subsequent "nodules" following the subcutaneous injection of trypsin. The subcutaneous injection of hyaluronidase alone caused no change; it was rapidly and completely diffused. The subcutaneous "nodules" and significant hexosamine changes which developed at the sites where trypsin was injected into a hyaluronidase-treated area closely resembled those which occurred with tryspin alone. Of interest is the significant leukocytosis which occurred *only* in those rabbits which received both hyaluronidase and trypsin.

THE GROUND substance of connective tissue contains a salt of an acidic substance which in water produces a highly viscous solution. This substance is presumably secreted by the connective tissue cells. Although it allows metabolites to pass through it, it has the important function of offering resistance to penetration by foreign matter such as infectious agents.[1-4] A complex mucopolysaccharide consisting of d-glucuronic acid and n-acetyl-d-glucosamine has been isolated from rabbit skin.[3-6] This compound has been called hyaluronic acid. That this mucopolysaccharide is not limited to the skin is evident by its presence in the following tissues: aqueous and vitreous humor,[7,8] Wharton's jelly of the umbilical cord,[9] synovial fluid,[10] pleural fluid,[11] fowl tumor,[12] and mucoid strains of Group A streptococcus.[9] It has been demonstrated that hyaluronic acid is depolymerized and hydrolyzed by enzymes classified as mucinases, of which hyaluronidase is one.[1-5] These mucinases are present in testes, some bacteria, and in the poisonous secretions of animals and reptiles.[1-3] A dramatic increase in the spreading of foreign material through connective tissue results from the action of the mucinase, hyaluronidase, on the substrate hyaluronic acid. The effect of hyaluronidase on hyaluronic acid in vitro "appears to go through three stages: (a) a separation of the protein residue, (b) a rapid depolymerizing action on the polysaccharide with diminution of the viscosity of aqueous solutions, and (c) a partial or complete hydrolytic action with liberation of n-acetyl-d-glucosamine and d-glucuronic acid."[1]

In view of these facts and also in view of the fact that a marked and significant increase in hexosamine-containing substance has been found to occur at the injection sites of crude and crystalline trypsin preparations,[13,14] it was decided to ascertain whether a single subcutaneous injection of hyaluronidase alone or the combined subcutaneous injections of hyaluronidase and trypsin would result in (a) "nodule" formation or other local tissue changes at the sites of injection, (b) other visceral lesions, (c) any significant tissue and/or plasma hexosamine changes, (d) any significant hematological changes.

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This Study was aided by grants from the American Legion and Helen Hay Whitney Foundation.

Materials and Methods

Twenty-two young male albino rabbits ranging in weight from 1.6 to 2.25 kilograms were employed in this study. The rabbits were obtained from the same source and fulfilled the same criteria regarding their genital state as those employed in the previous studies.[13, 14] These rabbits were subjected to the same procedures and treatment, except for the inoculant, as those employed in the previous investigations.

(70 mg.) of the substrate employed from 60 seconds to 15.4 seconds within four minutes.

Crystalline Trypsin. Twice-crystallized bovine trypsin was prepared as a 1 per cent solution in accordance with the method described in the previous studies.[13, 14] All solutions were Seitz filtered and bacteriologically checked for sterility before use. The proteolytic activity of these enzyme preparations was determined according to the method of Anson and Mirsky.[15] The methods for the measurement of the "nodules," the determination of the hexosamine content of the plasma and tissue, and the statistical treatment of the results which were employed in this study have been described in detail in the earlier reports. The animals employed as controls for this investigation are the same as those used in the previous studies.[13, 14] The hematologic studies performed in this problem were limited to red blood cell counts, white blood cell counts, and differential white blood cell counts. These observations were carried out throughout the entire study period on the blood obtained from the marginal ear veins of unanesthetized rabbits, before and after

Table 1.—*Relationship Between the Occurrence, Size of the "Nodule," and the Time Interval after a Single Subcutaneous Injection of Hyaluronidase, and following a Single Subcutaneous Injection of Crystalline Trypsin into a Hyaluronidase-Treated Area*

Key—Measurements (mm.)

Symbol	Length × Width × Height				Length × Width × Height		
0	0	0	0	to	1	1	1
±	1	1	1	to	3	3	2
+	3	3	2	to	6	6	3
2+	4	6	3	to	9	9	4
3+	9	9	4	to	12	12	4
4+	12	12	12	to	or over*		

* Maximum nodule observed 20 x 22 x 22 mm.

Inoculant	No. of Animals	Days Postinoculation												
		1	2	3	5	7	9	12	15	18	21	25	28	30
2% hyaluronidase solution	1 to 11	0	0	0	0	0	0	0	0	0	0	0	0	0
2% hyaluronidase plus 1% crystalline trypsin solution	12	0												
	13	0												
	14	0	0											
	15	0	0	0	±									
	16	0	0	±	±	+								
	17	0	0	+	+	+								
	18	0	0	0	±	+	2+							
	19	0	0	0	±	+	2+	3+						
	20	0	0	±	±	+	2+	3+						
	21	0	0	0	±	+	2+	3+	4+	4+	4+			
	22	0	0	±	±	+	2+	4+	4+	4+	4+	3+	2+	1+

*Hyaluronidase.** Bovine testicular hyaluronidase containing 144 turbidity-reducing units per milligram, according to Schering's assay, was prepared as a 2 per cent solution with physiologic saline and buffered with phosphate to a final pH 7.40. The activity of this preparation at the time of use was measured by the Ostwald viscometric method, using 0.5 per cent phosphate buffered potassium hyaluronate solution pH 7.40 as the substrate.[3] It was found that 1.0 ml. (20 mg.) of the hyaluronidase solution at 30° C. decreased the flow time of 7.0 ml.

* The hyaluronidase employed in this study was graciously donated by the Schering Corporation, Bloomfield, N. J.

receiving the inoculants. A Spenser Bright Line Hematocytometer was used for all counts. The blood smears for the differential white blood cell counts were stained with MacNeil's Tetrachrome stain.

Procedure and Results

In each of a series of eleven animals a single injection of 0.3 ml. of a 2 per cent hyaluronidase solution containing 6 mg. of the enzyme was subcutaneously introduced into a shaved area of the plantar surface of each of the hind legs, which is homologous to the human heel region. An immediate, rapid, and dramatic diffusion of the inoculant occurred in all the rabbits. No visible and/or palpable tissue change occurred at the injection sites at any time during the thirty-day experimental period in any of the animals except one (table 1). The exception was the development of a small superficial area of necrosis at one injection site in one animal on the third postinoculation day. The hexosamine content of the injection sites and other tissues such as the tendon of Achilles, which is subjacent to the inoculation site, and the skin covering the quadriceps femoralis, which is distant from the injection site, did not exhibit any significant deviation from the normal (table 2). The plasma hexosamine content, however, did exhibit a significant elevation (table 2). Concomitant hematologic studies demonstrated no significant change in the red cell counts, white blood counts, or differential counts (table 3). Thus, hyaluronidase per se failed to cause any macroscopic tissue change locally at the injection site, or any significant hematologic or tissue hexosamine changes other than the plasma hexosamine.

Table 2.—*Comparison of the Mean Hexosamine Content of the Injection Sites, "Nodules," Skin,* Tendon,† and Plasma following a Single Subcutaneous Injection of Hyaluronidase, and following a Single Subcutaneous Injection of Crystalline Trypsin into a Hyaluronidase Treated Area‡*

	Untreated	Inoculant	
		2% Hyaluronidase Solution	2% Hyaluronidase Plus 1% Crystalline Trypsin
Number of animals examined	30	11	11
Injection site and "nodules"			
Mean	5.16‡	5.49	6.78
σ	±0.66	±0.79	±0.33
t	—	1.08	8.90
Skin* over quadriceps femoralis			
Mean	4.14‡	4.22	4.56
σ	±1.04	±0.46	±0.91
t	—	0.27	0.80
Tendon† of Achilles			
Mean	4.13‡	3.94	3.97
σ	±0.76	±0.87	±0.69
t	—	0.54	0.53
Plasma			
Mean	51.4‡	70.6	65.7
σ	±6.80	±3.76	±13.11
t	—	9.85	2.67

‡ The plasma hexosamine is expressed as milligrams hexosamine per 100 ml. plasma. All other values are expressed as milligrams hexosamine per gram dry tissue, and cover the entire study period.

It is conceivable that trypsin, if given soon after a subcutaneous injection of hyaluronidase, may come in contact with and act on a greater amount of the same type of protein which gave rise to the "nodules," or perhaps come in contact with and act upon a new type of protein substrate. To learn whether trypsin introduced subcutaneously into tissues recently treated with hyaluronidase would result in (a) "nodule" formation or other local lesions, (b) other visceral lesions, (c) any significant tissue and/or plasma hexosamine changes, and (d) any significant hematologic alterations, the following study was instituted.

Three-tenths of a milliliter of a 2 per cent hyaluronidase solution containing 6 mg. of the enzyme was subcutaneously injected into a shaved area on the plantar aspect of each of the hind legs of a series of 11 rabbits. An immediate, complete, and dramatic diffusion of the inoculant occurred without any immediate or delayed local reaction. Twenty minutes later, 1.0 ml. of a 1 per cent crystalline trypsin solution containing 5 mg. of the enzyme (50 per cent of the enzyme preparation consists of magnesium sulfate), was subcutaneously injected into these very same areas. This inoculant diffused from the injection site almost as rapidly as did the hyaluronidase. This is in contrast to the very slow diffusion which occurred when trypsin alone was injected.[12]

Nevertheless, within five to seven days there appeared locally at each of the injection sites a distinct, firm, nontender, well-defined, elevated mass, which progressively increased in size to attain its maximum in fifteen to twenty days and then slowly regressed. At the termination of the thirty-day period of experiment, the masses, although small in size, were still present at the injection sites (table 1). At no time during the experimental period was there any evidence of erythema, fluctuation, necrosis, slough, breakdown, eschar, or fixation to the underlying tissue associated with the development of the "nodules." A significant elevation of the tissue hexosamine content occurred at the site of the subcutaneous injections of trypsin and hyaluronidase (table 2, fig. 1). It is to be noted (fig. 1) that the hexosamine elevation which occurred within twenty-four hours after inoculation persisted throughout the thirty-day experimental period. Other tissues such as the tendon of Achilles and the skin over the quadriceps femoralis did not exhibit any significant change in the tissue hexosamine content (table 2). A significant elevation of the plasma hexosamine content was likewise observed (table 2). The insignificant amount of hexosamine present in the inoculants could not account for the

TABLE 3.—*Comparison of Hematologic Changes in Rabbits following a Single Subcutaneous Injection of Hyaluronidase and following a Single Subcutaneous Injection of Crystalline Trypsin into a Hyaluronidase-Treated Area**

	No. of Animals Examined	Total No. of Counts Performed	R.B.C.† (millions)			W.B.C.‡ (thousands)		
			Mean	σ	t	Mean	σ	t
Untreated	36	36	5.64	0.90	—	7.19	2.28	—
2% hyaluronidase solution	11	17	5.01	0.76	0.82	8.21	1.45	1.96
2% hyaluronidase plus 1% crystalline trypsin solution	11	17	5.95	1.50	0.51	9.94	2.18	4.10

* All values cover the entire experimental period.
† Red blood cell count.
‡ White blood cell count.

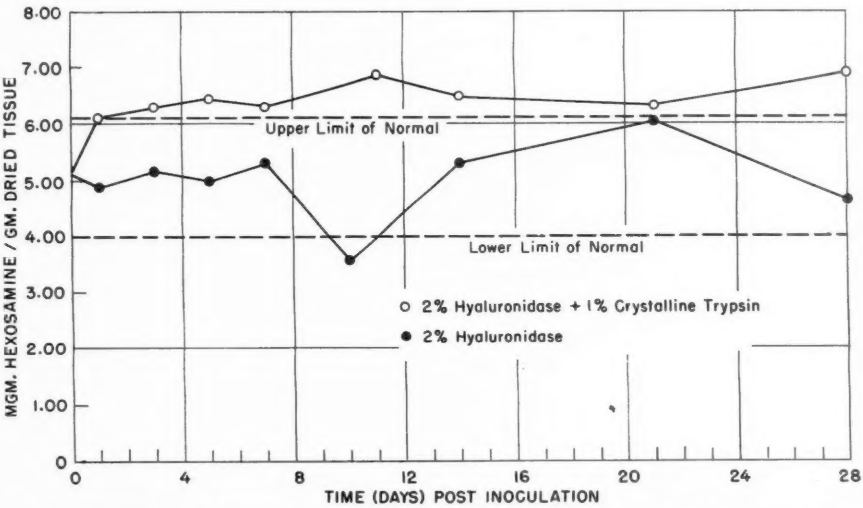

FIG. 1.—Comparison of hexosamine contents of injection sites and "nodules" following a single subcutaneous injection of hyaluronidase, and following a single subcutaneous injection of crystalline trypsin into a hyaluronidase-injected area.

hexosamine changes noted. The entire inoculating dose of crystalline trypsin contained 0.006 mg. hexosamine, and that of hyaluronidase contained 0.0018 mg. hexosamine. The injection sites and "nodules" exhibited an increase in hexosamine content, averaging forty times the hexosamine content of the inoculant. Of particular interest is the fact that these rabbits exhibited a leukocytosis which was significantly elevated above the normal (table 3). However, there was no significant change in the red blood cell counts or differential counts.

Discussion

The rapid, dramatic, and complete diffusion of the subcutaneously injected hyaluronidase is in Meyer's opinion due to the "depolymerization of the hyaluronate gel, either by the hydrolysis of the glucosaminidic linkage or by hydrolysis of the anhydride linkages."[4] Other than this, subcutaneously injected hyaluronidase did not give rise either to any macroscopic tissue change, or to any significant tissue hexosamine alteration either locally or elsewhere, nor were there any significant hematologic changes. An outstanding exception to these findings is the significant elevation of the plasma hexosamine content which occurred in those animals treated with hyaluronidase alone. This observation points out the lack of any necessary correlation between the changes of the plasma hexosamine and the hexosamine contents of the tissues studied. Similar plasma results were noted in the animals treated with chymotrypsin, lysozyme, or bovine serum albumin.[13]

The subcutaneous "nodules" which developed at the sites where crystalline trypsin was injected into a hyaluronidase-treated area were macroscopically very similar to those which occurred following the subcutaneous injection of trypsin alone.[12] In addition, the developmental course of these "nodules" was very similar to that which occurred in the animals inoculated with trypsin alone, as evidenced by the fact that in rabbits treated successively with hyaluronidase and trypsin, the "nodules" appeared in five to seven days, and reached their maximum size in fifteen to twenty days (table 1). In the series treated with trypsin alone, "nodules" developed in four to seven days and attained their maximum size in fourteen to eighteen days.[12] Another feature common to both these series was the significant elevation of the plasma hexosamine.

Another very interesting observation noted in the rabbits which were treated with both hyaluronidase and trypsin was the significant increase in the white blood cells (table 3). No significant alteration of the red cell count or differentials occurred.

In view of the fact that hyaluronidase per se did not elicit any significant hematologic response, and particularly in view of the fact that the two groups of rabbits of this study, except for the addition of a second inoculant to one group, were subjected to and maintained under the same conditions and treatment, it would appear that the leukocytosis was somehow related to the enzyme trypsin. Evidence in favor of this view is the observation that similar hematologic changes occurred in rabbits which received trypsin either subcutaneously or intravenously, whereas saline did not provoke any significant hematologic change.[16]

It is a matter of conjecture whether chondroitin sulfate, a second mucopolysaccharide present in skin,[4, 5] which is, according to Meyer,[4] "firmly bound to protein" and "hydrolyzed by testicular hyaluronidase to varying degrees," played any part in the results obtained.

The fact that the hyaluronidase preparation is completely devoid of any proteolytic activity, as determined by the Anson-Mirsky method,[15] adds weight to the view that the "nodule" formation, significant hexosamine changes of the injection sites and "nodules," and significant white blood cell count increase were somehow related to the proteolytic enzyme, trypsin.

Summary

1. Five to seven days following a single subcutaneous injection of 1.0 ml. of a 1 per cent crystalline trypsin solution into the plantar aspect of the hind legs of rabbits which were previously inoculated with 0.3 ml. of a 2 per cent hyaluronidase solution, there developed at the injection sites distinct, firm, nontender, elevated masses.

2. The "nodules" progressively increased in size to reach their maximum in fifteen to twenty days postinoculation.

3. At no time during the developmental course of these "nodules" was there any evidence of erythema, tenderness, eschar, necrosis, breakdown, fluctuation, or fixation to the underlying tissue.

4. A significant increase in the hexosamine content of the injection sites and of the "nodules" which subsequently developed was observed to occur soon after the injection of crystalline trypsin into the hyaluronidase-treated area and persisted throughout the thirty-day period of observation.

5. A significant increase in the white blood cell count, unassociated with any significant change in the red blood cell count or differential count, was observed to occur only in those rabbits which received the subcutaneous injections of both hyaluronidase and trypsin.

6. The subcutaneous injection of 0.3 ml. of a 2 per cent hyaluronidase solution, with one exception, did not give rise to any macroscopic tissue changes or tissue hexosamine changes, either locally or elsewhere. The one exception was the occurrence of a small superficial area of necrosis at one injection site in only one animal.

7. The occurrence of a significant elevation of the plasma hexosamine in the group which did not exhibit any significant tissue hexosamine change illustrates the lack of any necessary correlation between the plasma and tissue (studied) hexosamine following the subcutaneous introduction of the test substance.

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QRS-T Patterns in Multiple Precordial Leads that May Be Mistaken for Myocardial Infarction

I. Left Ventricular Hypertrophy and Dilatation

By Gordon B. Myers, M.D.

The electrocardiograms of patients in whom myocardial infarction was excluded at autopsy are presented to bring out the following features of left ventricular hypertrophy that may be mistaken for myocardial infarction: (1) QS patterns and/or abnormal RS–T elevation in leads from the right precordium; (2) abnormal Q waves, multiphasic QRS and/or cove plane inversion of the T waves in leads from the transitional zone; (3) prominent Q waves, marked RS–T depression and/or sharply inverted T waves in leads from the left axilla.

A DETAILED analysis of the electrocardiographic findings in 161 cases of pathologically established myocardial infarction has been presented,[1–7] but little attention was devoted to differential diagnosis. Full consideration of the subject requires presentation of cases with electrocardiographic findings suggestive of myocardial infarction but without evidence of such at autopsy.

Fifty cases have been selected for presentation because of abnormalities in the QRS and/or RS-T complex in Wilson precordial leads that might be mistaken for aberrations due to myocardial infarction. In all cases autopsy was performed and in none of the subjects was there pathologic evidence of myocardial infarction or of focal subendocardial myomalacia of the type attributed to coronary insufficiency by Master and associates.[8] Postmortem examination included injection of the coronary arteries with radiopaque mass, roentgenogram, and subsequent dissection according to a previously described technic in 42 of the cases (all except Cases 3, 5, 20, 21, 33, 34, 36, 44).[9] A large number of microscopic blocks was studied in many cases, in order to make certain that the possibility of myocardial infarction could be excluded.

The absence of pathologic evidence of myocardial infarction, however, does not rule out a coronary origin for the electrocardiographic findings. Blumgart, Gilligan, and Schlesinger[10] produced temporary coronary occlusion in dogs and demonstrated electrocardiographic patterns typical of myocardial infarction in animals that showed no gross or microscopic evidence of a myocardial lesion at subsequent necropsy. Bohning and Katz[11] reported one patient with serial changes in Lead CF_2, considered diagnostic of a rapidly healing anteroseptal infarction, whose autopsy study two years later showed narrowing of both coronary arteries, but no evidence of occlusion or infarction.

A definite electrocardiographic diagnosis of myocardial infarction had been made during life in 7 cases from this series (Cases 12, 17, 27, 28, 31, 38, 41); a diagnosis of probable infarction was made from the first tracing in Cases 11 and 49, and the possibility of infarction could not be positively excluded in several others. Upon reconsideration, after completion of the pathologic studies, it was concluded that the electrocardiographic findings had been misinterpreted in all but one of the foregoing cases and were explicable upon a basis other than myocardial infarction or the situation encountered by Blumgart and associates and by Bohning and Katz. The findings in Case 12 were not satisfactorily accounted for at autopsy and it is believed that an infarct was missed patholo-gi-

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cally because of an inadequate number of microscopic blocks.

The electrocardiographic patterns which may be mistaken for those of myocardial infarction include (1) left ventricular hypertrophy and dilatation, (2) right ventricular hypertrophy, (3) right ventricular dilatation, (4) left bundle branch block, (5) right bundle branch block, (6) alterations in blood potassium, (7) myocardial ischemia, (8) pericarditis and subepicardial myocarditis, and (9) arrhythmias causing QRS distortion. The presentation of a sufficient number of cases for each of the foregoing nine groups was found too voluminous for a single manuscript. As a consequence, the study has been divided into four parts. The electrocardiographic features of left ventricular hypertrophy and dilatation that may be mistaken for those of myocardial infarction are considered in this article; the differentiation from right ventricular hypertrophy and dilatation, in the second; and the features of bundle branch block that may be confused with infarction, in the third; and the diagnostic errors that may be made in the presence of alterations in blood potassium, myocardial ischemia, pericarditis, subepicardial myocarditis, and arrhythmias causing QRS distortion are considered in the final manuscript.

Electrocardiographic Features Diagnostic of Left Ventricular Hypertrophy

Left axillary and precordial leads facing the epicardial surface of an hypertrophied left ventricle characteristically display:[12, 13] (a) prominent R wave with slightly prolonged ascending limb and slightly delayed peak, usually preceded by a small Q wave less than 25 per cent of the amplitude of the R; (b) depression of the RS-T junction, accompanied by an inverted, diphasic, or flattened T wave. Right precordial leads facing the epicardial surface of the right ventricle or right atrium characteristically display: (a) minute R wave and abnormally deep and prolonged S wave; (b) elevated RS-T junction and tall upright T wave.

Electrocardiographic Features of Left Ventricular Hypertrophy that May Be Mistaken for Those of Myocardial Infarction

The precordial electrocardiogram of uncomplicated left ventricular dilatation and hypertrophy may be mistaken for that of myocardial infarction because of: (A) exaggeration of the normal Q wave in left ventricular leads; (B) an RS-T pattern in left ventricular leads, characterized by either: (1) sharp inversion of the T wave accompanied by a slightly elevated or isoelectric RS-T junction instead of the customary slight depression, (2) marked RS-T depression, (3) deeper inversion of the T wave in Lead V_4 than in V_5 or V_6, or (4) rapid changes in serial tracings; (C) QS deflections in Leads V_1 and V_2; (D) abnormal elevation of the RS-T junction in leads from the right side of the precordium; (E) bizarre QRS patterns in leads from the transitional zone, consisting of: (1) a multiphasic complex, (2) an abnormal initial downstroke; (F) abnormal RS-T complex at the transitional zone, including cove inversion of the T wave. These features are collectively illustrated by the electrocardiograms reproduced in figures 1, 2, and 3, obtained in Cases 1 to 12, inclusive. Autopsy revealed left ventricular hypertrophy without infarction and without coronary occlusion or narrowing in ten of these patients and a normal heart in the other two patients (Patients 2 and 11). The electrocardiograms of the two latter patients were reproduced in figures 1, *B* and 3, *A*, respectively, because of Q waves in Lead V_4 that could be mistaken for those due to myocardial infarction.

Exaggeration of the Normal Q Wave in Left Ventricular Leads. Q waves are present in Lead V_6 in the majority of normal subjects,[9, 14] and represent negative potentials transmitted from the endocardial surface of the left side of the septum and anteroapical wall of the left ventricle through the intervening structures to the axilla during the brief period that normally elapses before the impulse reaches the subendocardial layer of the lateral wall. The normal Q wave in left ventricular leads V_4, V_5, and V_6 is almost always less than 3 mm. in depth and invariably less than 25 per cent of the amplitude of the succeeding R wave.

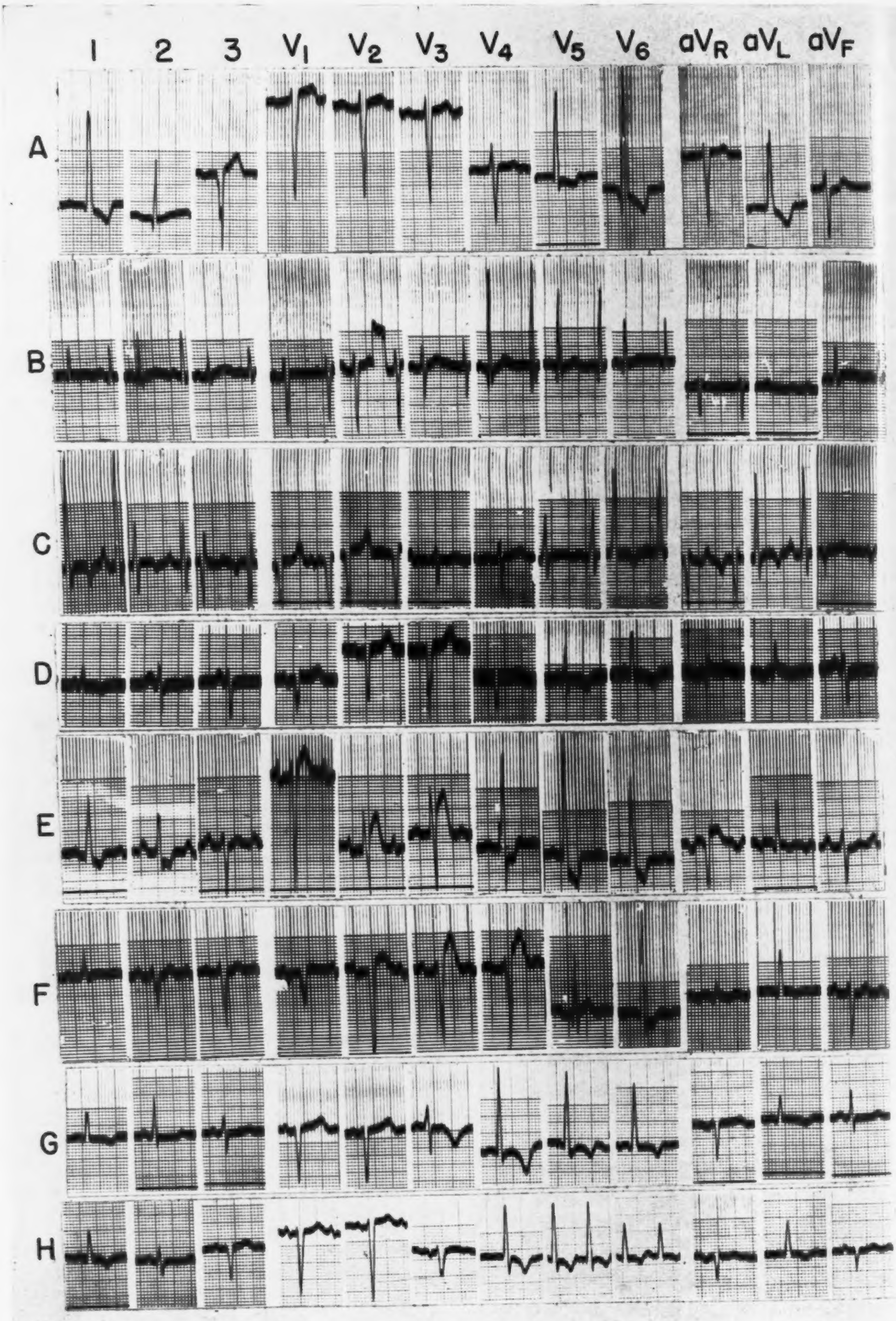

FIG. 1.—Left ventricular hypertrophy with electrocardiographic features suggestive of myocardial infarction. *A*, Case 1; *B*, Case 2; *C*, Case 3; *D*, Case 4; *E*, Case 5; *F*, Case 6; *G*, Case 7; *H*, Case 8.

Q waves of similar origin are present in Leads V_5 and V_6 in uncomplicated left ventricular hypertrophy[12, 13] and may be exaggerated in amplitude as a result of: (1) the obtained from Patient 1, a 26 year old man with rheumatic mitral and aortic insufficiency complicated by subacute bacterial endocarditis. The Q wave in Lead V_6 from this patient ranged

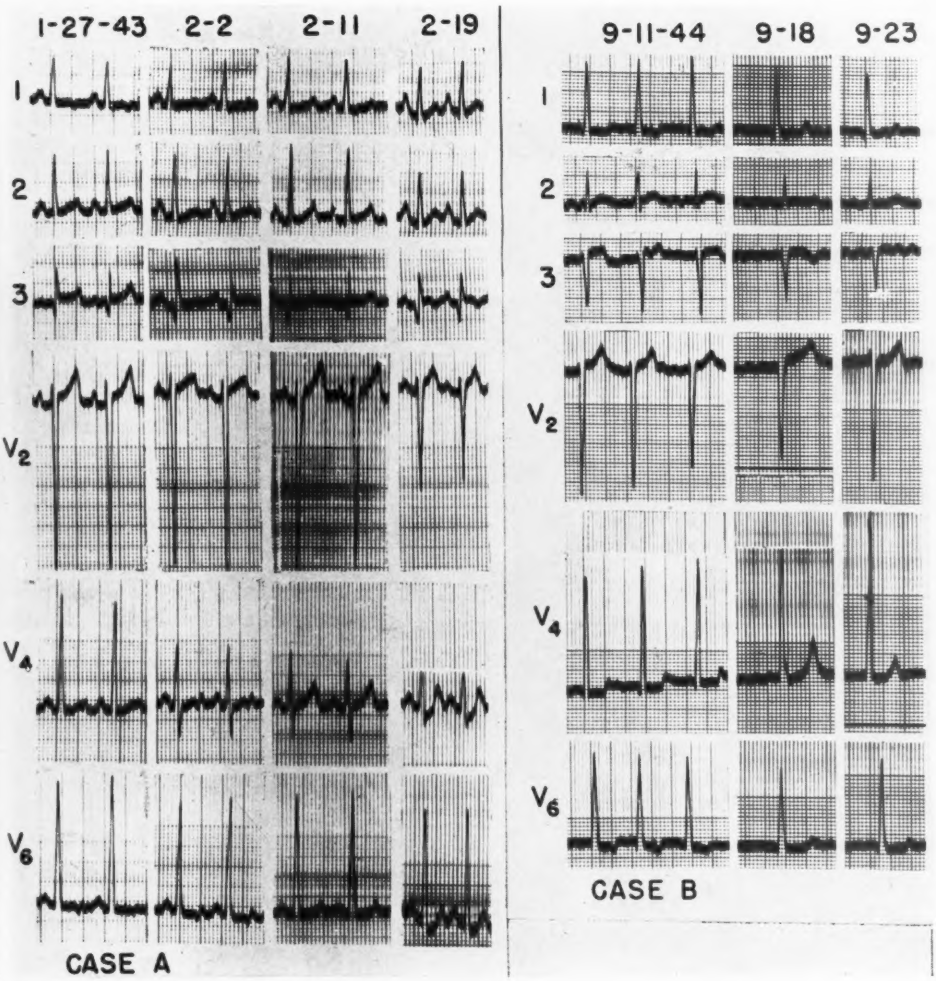

Fig. 2.—Left ventricular hypertrophy and dilatation with serial changes in RS-T pattern suggestive of myocardial infarction. *A*, Case 9; *B*, Case 10.

greater voltage developed during activation of the hypertrophied septum, and (2) the improved transmission to the axilla because of the closer approach of the enlarged left ventricle to the thoracic cage. This is exemplified by the electrocardiogram reproduced in figure 1, *A* from 6 to 7 mm. in depth and was thus comparable in absolute voltage to the Q wave recorded in this lead as a manifestation of anterolateral infarction.[2] However, the QRS pattern in Lead V_6 of figure 1, *A* could be recognized as a manifestation of left ventricular hypertrophy, rather

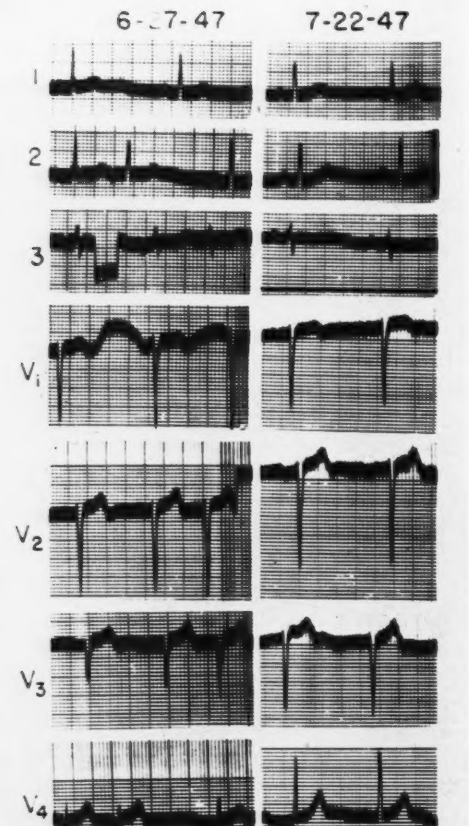

FIG. 3.—Serial electrocardiograms in Case 11 (*A*, above) and in Case 12 (*B*, facing page).

than infarction, by the normal duration of the Q wave and by the exceptionally tall and abnormally prolonged ascending limb of the succeeding R wave. The upstroke ranged from 35 to 38 mm. in amplitude, thereby making a normal QR ratio of 15 to 20 per cent. The antemortem interpretation, based on Q duration and QR ratio in V_6, was confirmed at autopsy, which revealed rheumatic mitral and aortic insufficiency and subacute bacterial endocarditis with marked left ventricular hypertrophy, but without coronary disease or myocardial infarction.

Among a series of 1375 patients studied with multiple precordial leads and subsequently studied at autopsy, no case without pathologically demonstrable infarction has been encountered thus far in which the Q wave in left ventricular lead V_6 exceeded 0.03 second from onset to nadir, and 25 per cent of the amplitude of the subsequent R wave.* On the other hand, infarction confined to the subendocardial layer of the anterolateral wall may be accompanied by Q waves that are within normal limits, both as to duration and as to QR ratio. Whenever Q waves in the customary left ventricular leads approach the border line in duration or in relative amplitude, a repetition of the tracing, including high precordial leads, is advisable to investigate the possibility of a high anterolateral infarct producing marginal zonal patterns in the customary leads.[7]

The amplitude and duration of the normal Q wave are usually greater in Lead V_6 than in V_5 and are, in turn, greater in V_5 than in V_4. Case 2, figure 1, *B* is included because the Q wave measured 6.0 mm. in V_4, 4.0 mm. in V_5, and 2.5 mm. in V_6. Although such relationships raise the question of anteroseptal infarction,[1] the absolute amplitude of the Q wave loses its significance in this case when attention is directed to the time from onset to nadir of the downstroke and to the relative heights of the R waves in the three leads. The duration of the Q wave and the QR ratio are almost identical in Leads V_4, V_5, and V_6 and are within the limits

* This statement is made subject to the condition that Lead V_6 reflects the potential variations of the left ventricle, because of the occasional finding of a QS pattern in V_6 owing to the axillary transmission of the potential variations of a dilated right ventricle in a heart rotated markedly in a clockwise direction.

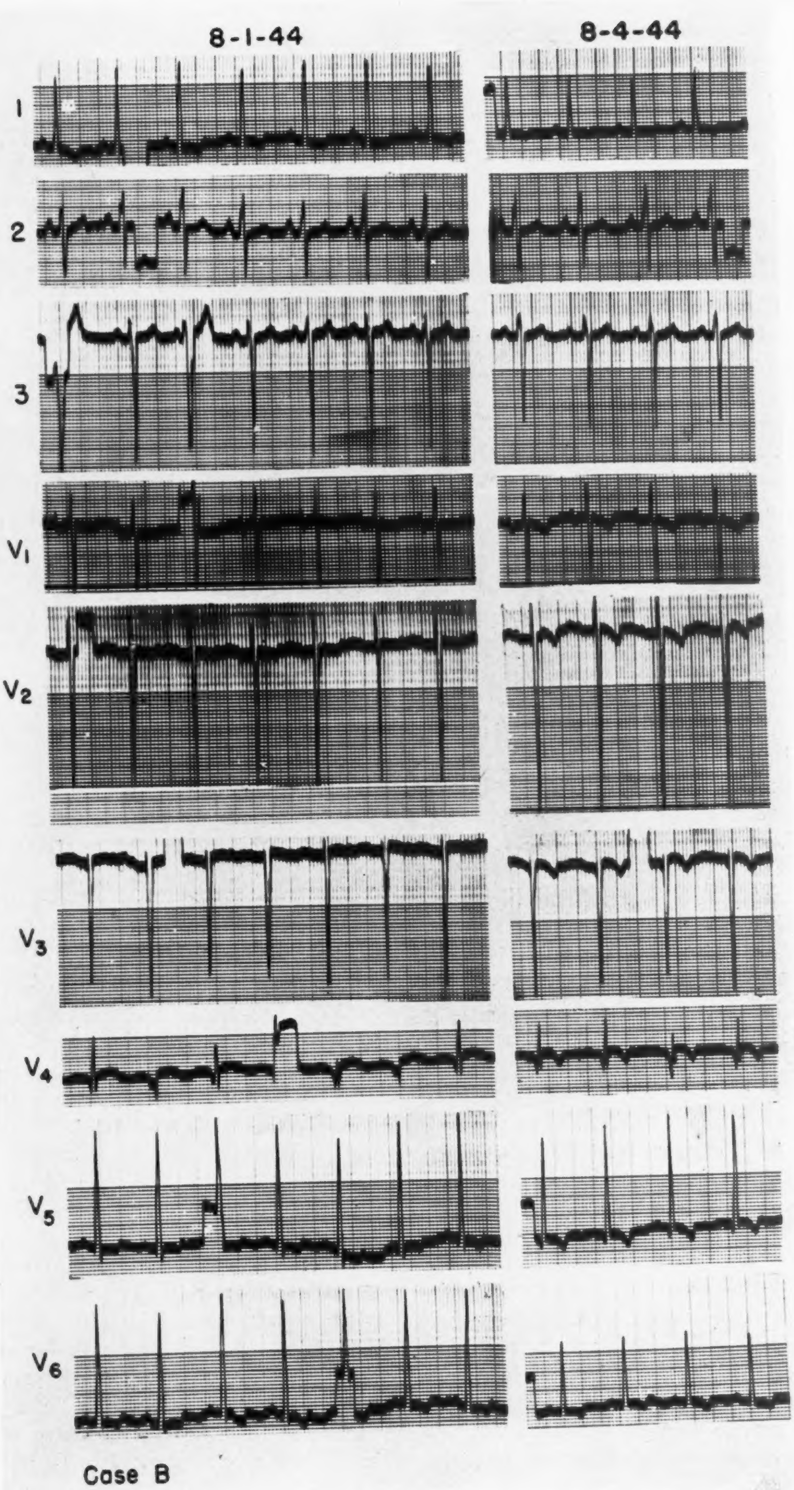

FIG. 3.—*Cont'd.*

of normal. The interpretation, based on these two latter criteria, was confirmed by the finding of a normal heart at autopsy. Death was due to carcinoma of the colon. The parallel decrease in amplitude of the Q and R deflections as the electrode was moved from the V_4 position into the axilla was a manifestation of the normal loss of potential with increasing distance from the cardiac border.

Suggestive RS-T Patterns in Left Ventricular Leads. The typical findings in leads facing the epicardial surface of the anterolateral wall of an hypertrophied left ventricle are slight to moderate depression of the RS-T junction and inverted to diphasic T waves, as illustrated by Lead V_5 of figure 1, *H* and Lead V_6 of the tracing taken on February 2 in figure 2, *A*. Four of the more common variants which may be mistaken for myocardial infarction are illustrated in figures 1 and 2 and will be discussed separately.

Sharp Inversion of the T Wave, Accompanied by an Isoelectric or Even Slightly Elevated RS-T Junction: This may occur in association with left ventricular hypertrophy and may mimic the cove negative T waves associated with myocardial infarction. This is illustrated by the T waves in Leads V_5 and V_6 of figure 1, *D* and those in V_6 and aV_L of figure 1, *C*. These tracings were obtained from Patients 3 and 4, respectively, neither of whom had received digitalis.

Lead aV_L of figure 1, *C* exhibited the combination of upward bowing of the RS-T segment and V-shaped inversion of the T wave, resulting in the cove curvature originally considered diagnostic of myocardial infarction, but now identified with other lesions of the subepicardial layer of the myocardium. The tall initial R wave in these leads excluded the possibility of a central zone of transmural infarction and a marginal zone of subendocardial infarction in the area subtended by the electrode, but was compatible with any of the following three possibilities: (a) infarction limited to the subepicardial layer of the lateral wall, (b) marginal zone of subepicardial ischemia beyond the boundary of a high lateral infarct, (c) pericarditis or subepicardial myocarditis. The latter alternative was in keeping with the clinical picture and was subsequently confirmed at autopsy. The patient's death was due to uremia secondary to malignant hypertension and the heart showed left ventricular hypertrophy complicated by subepicardial lesions typical of uremic myocardiopathy. The coronary arteries were patent and no gross or histologic evidence of infarction was found.

The contour of the T wave in Leads V_5, and V_6 of figure 1, *D* was less typical, though compatible with a specific lesion of the subepicardial layer, but was more in keeping with uncomplicated left ventricular hypertrophy. In view of the abnormally small R waves in V_3, and V_4, the possibility that the prominent initial R and inverted T waves of Leads V_5, and V_6 reflected the potential variations of the marginal zone beyond the boundary of the high anterolateral infarct should have been investigated by high precordial leads; however, this possibility was excluded by postmortem examination. The patient died of cerebral hemorrhage six months after the electrocardiogram was made and autopsy revealed uncomplicated left ventricular hypertrophy of hypertensive origin.

Marked RS-T Depression in Left Ventricular Leads: Marked RS-T depression in left ventricular leads that might be mistakenly interpreted as due to subendocardial ischemia or infarction[2, 7] may occur in uncomplicated left ventricular hypertrophy as a result of: (a) digitalis effect, (b) coexistence of high P waves and tachycardia.

The changes produced by *digitalis* in left ventricular leads are well known and consist in depression of the RS-T junction, straight downward sloping of the RS-T segment, steep ascent of the terminal limb of the T wave, and shortening of the Q-T interval. The extreme degree of RS-T depression that may occur in left ventricular leads due to the combination of left ventricular hypertrophy and full digitalization is illustrated in figure 1, *E* (Case 5). The RS-T junction was depressed 6 mm. below the isoelectric line in Lead V_5 and 3.5 mm. in V_4 and V_6. Even without benefit of history, the RS-T depression can be attributed to digitalis, rather than to subendocardial ischemia or infarction, because of the characteristic shape of the T wave and the distinct shortening of the QT interval. The patient was admitted to the hos-

pital with congestive failure and was digitalized before the electrocardiogram was made, but died on the following day. Autopsy revealed a huge heart, weighing 1,000 grams, the enlargement being due principally to left ventricular hypertrophy of hypertensive origin. No evidence of infarction, coronary occlusion, or narrowing was found.

When marked RS-T depression occurs in the absence of certain of the classical manifestations of digitalis, confusion may result, as illustrated by figure 1, *F* (Case 6). The patient had been admitted to the hospital with marked congestive failure, due to rheumatic aortic stenosis and insufficiency, and had received digitalis before the electrocardiogram was made. The 3-mm. depression of the RS-T junction and the straightening of the RS-T segment in Lead V_6 could be explained by digitalis action in the presence of left ventricular hypertrophy, but the contour of the T wave in both V_6 and left ventricular lead aV_L and the Q-T interval near the upper limits of normal[15] were atypical of digitalis effect. Postmortem examination revealed a 787-gram heart with a markedly hypertrophied left ventricle and a very distended, but thin-walled, right ventricle. Advanced aortic stenosis was present, but the coronary tree was widely dilated and there was no evidence of infarction. An acute epicarditis and subepicardial myocarditis was demonstrated microscopically and accounted for the modifications in RS-T pattern.

Coexistence of a *deep auricular T wave* and *tachycardia* may lead to marked pseudodepression of the RS-T segment,[9] that could be mistaken as evidence of subendocardial ischemia or infarction. This is exemplified by Leads V_4 through V_6 of the tracing of February 19 in figure 2, *A* and will be discussed below.

Deeper Inversion of the T Wave in Lead V_4 Than in V_5 and V_6: This finding, as in figure 1, *G* and *H*, may arouse the suspicion of anteroseptal infarction. These tracings were obtained from Patients 7 and 8, respectively, neither of whom had received digitalis previously. The possibility of a transmural anterior infarct was excluded in both cases by the insignificant Q wave and tall R wave in left ventricular leads. Acute infarction limited to the subendocardial layer was ruled out by QRS pattern and the lack of sufficient RS-T depression. On the other hand, the possibility of infarction or inflammation limited to the subepicardial layer was excluded by the fact that the RS-T junctions were depressed rather than elevated or isoelectric. The RS-T patterns in Leads V_4 through V_6 of both patients were therefore ascribed to left ventricular hypertrophy. The progressive diminution in the depth of the inverted T wave as the electrode was moved from the C_4 to the C_6 position was attributed to loss of potential with increasing distance from the heart. This explanation was strongly supported in Case 7 (fig. 1, *G*) by the parallel diminution in the amplitude of the R wave. A concurrent reduction in amplitudes of the R and T waves was also noted in Case 8 when the electrode was moved from precordium to midaxilla, but not when it was shifted from the C_4 to the C_5 position. The T wave in V_4 was slightly deeper than that in V_5, but the R wave in V_4 was not quite as tall as that in V_5.

Patient 7 had no symptoms referable to the heart and died of carcinoma of the colon. Patient 8 was admitted to the hospital with congestive failure and expired suddenly of pulmonary embolism. Autopsy revealed left ventricular hypertrophy of hypertensive origin in both patients, without infarction or coronary narrowing. Thus deeply inverted T waves that progressively diminish as the electrode is moved from the C_4 to the C_6 position may occur as a manifestation of uncomplicated left ventricular hypertrophy and are usually, though not necessarily, accompanied by parallel decrease in the amplitude of the R waves.

Rapid Changes in RS-T Segment and T Waves of Left Ventricular Leads in Serial Tracings: These often arouse the suspicion of myocardial infarction, but may occur in association with left ventricular dilatation and hypertrophy without demonstrable myocardial lesion, particularly when the heart is subjected to some extrinsic stress. This is exemplified by figure 2, which reproduces the serial electrocardiograms of two patients with thyrotoxicosis and associated left ventricular dilatation and hypertrophy.

Patient 9 (fig. 2, *A*) was a 34 year old woman

with severe Graves' disease. The tracing of January 27, 1943, obtained when the basal metabolism rate was +80, showed very tall R waves in Leads V_4 and V_6, which were of normal duration and thus not diagnostic of left ventricular hypertrophy. In Leads V_6 and I, the RS-T segment was slightly depressed and the T wave, inverted, whereas in Lead V_4 the T wave was coarsely notched. Subsequent electrocardiograms showed significant changes in the RS-T segments and T waves, but not in the QRS complexes. The tracing of February 2, obtained when the basal metabolism rate had fallen to +51 under iodides, showed a diphasic wave in Lead V_6, a doubled T wave in V_4, and flattened T wave in Lead I. Although the basal metabolism rate did not decrease further, the record of February 11 showed normal upright, pointed T waves in all leads. Cardiac glycosides could be positively excluded as a cause of the RS-T changes, since none was given to this patient at any time. Because of the absence of significant changes in the QRS complexes, the RS-T evolution in the tracings made between January 27 and February 11 was much more likely due to subsidence of external stress upon the left ventricle than to healing of a small myocardial infarct.

Thyroidectomy was performed on February 17 and was complicated by a postoperative thyroid crisis. Electrocardiogram on February 19, obtained during the crisis, showed a sinus tachycardia of 154 and striking changes in the RS-T segment of Leads III, V_4, and V_6, without significant alterations in QRS. Although the QRS-T pattern in Lead III was strongly suggestive of recent posterior infarction, the diagnosis is not justified unless parallel changes can be demonstrated in Lead II and particularly in Lead aV_F.[5] Lead aV_F was not obtained on this patient, but the findings in Lead II failed to confirm the presence of posterior infarction. The apparent RS-T depression in Leads V_4, and V_6 might have represented a reciprocal effect of a recent posterior infarction or a direct effect of acute ischemia or infarction limited to the subendocardial layer of the anterolateral wall; however, the contour of the RS-T segment and T wave was not typical of either of these alternatives. More careful study showed that the depression was apparent, rather than real, and was due to two factors: (1) the presence of a tachycardia sufficient to cause superimposition of the P wave on the antecedent T and thereby prevent the usual diastolic return of the string to the isoelectric line, (2) a prominent auricular T wave following an exceptionally tall P wave.[9]

The patient died on February 23 and autopsy disclosed a 420-gram heart, showing left ventricular hypertrophy, ascribed to thyrotoxicosis, after failure to demonstrate evidence of hypertension or other recognized causes. The coronary vessels were normal and no evidence of infarction was found in either the posterior or the anterolateral walls. The postmortem findings were thus in keeping with the electrocardiographic interpretation. The QRS-T pattern in Lead III was probably derived principally from its left arm component. Although Lead aV_L was not obtained, the findings in Lead I suggested that the potential variations of the left arm paralleled those of the V_4, and V_6 positions. Thus the Q wave, elevated RS-T junction, and inverted T wave of Lead III represented, respectively, the reciprocals of the prominent R wave, depressed RS-T junction, and upright T wave, which should have been recorded in Lead aV_L.

The patient whose electrocardiograms are reproduced in figure 2, *B* (Case 10) was admitted to the hospital with thyrotoxicosis complicated by auricular fibrillation, congestive failure, and right lower lobar pneumonia and received 1.6 Gm. Cedilanid prior to the electrocardiogram of September 11, the second hospital day. The QR pattern in Leads V_4 and V_6 was indicative of left ventricular hypertrophy. The inverted T waves of Leads V_6 and I and the diphasic T wave of V_4 were probably not due exclusively to digitalis, because of the subsequent appearance of upright T waves in these leads despite continuation of digitalis in doses sufficient to maintain the apical rate between 50 and 60. The improvement in the T waves was in keeping with decrease in load upon the left ventricle, consequent upon recovery from the pneumonia, and decrease in the thyrotoxicosis.

Thiourea was employed and the course was complicated by a toxic psychosis, which led to

death on October 14. The heart weighed 478 grams and showed left ventricular hypertrophy, believed to have been due to hyperthyroidism because of the failure to find evidence of hypertension or other known causes. The coronary vessels were normal and the myocardium showed no evidence of infarction. Thus, the serial changes in the T waves were not due to coronary disease.

QS Deflections in Leads V_1 and V_2 (Fig. 1, C, D, F). Such deflections may raise the question of infarction of the interventricular septum,[4] but are not diagnostic of a septal lesion because of their occasional presence in normal subjects,[9] and in persons with left ventricular hypertrophy.[16] The registration of a QS complex in Leads V_1 and V_2 as a normal variant is favored by a cardiac rotation that brings the right atrium beneath the sternum, carries the left apex backward, and tilts the mitral orifice to the right and forward, thereby facilitating transmission of left ventricular cavity potentials through the interatrial septum to the precordium. Conditions suitable for the registration of a QS deflection as a normal variant were present in Patients 4 and 6 (fig. 1, *D*, *F*), as shown by (1) distinct auricular intrinsicoid deflections in Leads V_1 and V_2, indicating proximity of the electrode to the right atrium; (2) prominent late R waves in Lead aV_R, indicating backward displacement of the left apex.[17, 18] While the apparent relation of the electrode to the heart was strongly in favor of interpreting the QS complex of Patients 4 and 6 as a normal variant, it did not positively exclude the possibility of septal infarction. On the other hand, the absence of demonstrable backward rotation in Lead aV_R of Patient 3 did not rule out positional factors as the cause of the QS in Leads V_1 and V_2 of figure 1, *C*.

When there is uncertainty as to the significance of QS complexes in V_1 and V_2 the following additional steps are advisable: (1) search for evidence of infarction in precordial leads to the left and right, (2) repetition of the tracing in a different posture to determine the stability of the QS pattern in Leads V_1 and V_2. The findings in leads to the left of V_2 were not diagnostic of infarction in any of the three cases, but the abnormal elevation of the RS-T junction in Leads V_3 and V_4 of Patient 6 and the abnormally small initial R wave in the same leads of Patient 4 warranted further investigation. The abnormal RS-T displacement in Leads V_3 and V_4 of Patient 6, figure 1, *F*, was referable to an epicarditis, as discussed above. Lead V_{3R} was obtained from Patient 4 and revealed a QS complex similar to that in Lead V_1, figure 1, *D*. This represented the expected finding if the QS pattern in V_1 and V_2 were a normal variant. The tracings reproduced in figure 1, *D*, *F* were obtained with the patients in the sitting position. Repetition with the patients in the recumbent position revealed a distinct initial R wave in the first two precordial leads in Case 6, a small initial R wave in V_1 and V_2 in Case 4, and a somewhat larger initial R wave in Leads V_3 and V_4. This confirmed the interpretation of the QS complexes in V_1 and V_2 of Cases 4 and 6 as a normal variant referable to cardiac position. On autopsy, no evidence of infarction of the septum was found in these two cases or in Case 3.

Elevation of the RS-T Segment in Right Precordial Leads. This is an expected finding in left ventricular hypertrophy and should not be misinterpreted as evidence of myocardial infarction when the segment maintains its normal upward concavity and the T wave is upright and normal in shape, as in figure 1, *C*, *D*, *G*, *H*. Excessive elevation of the RS-T segment in right precordial leads sufficient to arouse the suspicion of infarction may occur in association with left ventricular hypertrophy as a result of (1) digitalization, (2) superimposed pericarditis.

The combined effects of digitalis and left ventricular hypertrophy on the RS-T segment and T wave in right precordial leads may mimic those associated with acute anteroseptal infarction, as exemplified by figure 1, *E* (Case 5). Inspection of the first three precordial leads revealed the following changes suggestive of acute anteroseptal infarction: (a) marked RS-T elevation, amounting to 4 mm. in V_1, 5 mm. in V_2, and 8 mm. in V_3; (b) straightening of the RS-T segment; (c) precipitous descent of the T wave. However, the possibility of anteroseptal infarction was rendered very unlikely by the prominent initial R waves, measuring 4 mm.

in V_1, 10 mm. in V_2, and 13 mm. in V_3, and was excluded as a result of other evidence indicating that the RS-T patterns in V_1 through V_3 were referable to digitalis action, namely: (a) the shortening of the Q-T interval, (b) the fact that the RS-T complex in V_1 through V_3 was reciprocal to the digitalis RS-T pattern in V_5 and V. As indicated above, autopsy revealed left ventricular hypertrophy without infarction and thus confirmed this interpretation.

Although Patient 6 had left ventricular hypertrophy and had received digitalis prior to the electrocardiographic recording (fig. 1, *F*), the findings in the first four precordial leads could not be satisfactorily explained by this combination because the extreme upward RS-T displacement in right ventricular leads V_3 and V_4 was disproportionate to the slight elevation in right atrial lead V_1 and to the depression in V_6. It was therefore necessary to consider the possibility that an acute anteroseptal infarct may have caused the RS-T elevation in V_3 and V_4 and may have produced reciprocal depression in V_6. High precordial leads were taken, but revealed a small R, deep S, and elevated RS-T segment comparable to that in Leads V_3 and V_4. Anteroseptal infarction could not be ruled out by the absence of a diagnostic QRS pattern in a single tracing, but its possibility was excluded in this case by a study of previous electrocardiograms. The first tracing, made eight days prior to that in figure 1, *F*, showed RS-T depression in V_6, typical of digitalis action, but no abnormal elevation in right ventricular leads. The latter was first noted two days later and steadily increased in two intervening records, to reach a maximum in the tracing reproduced in figure 1, *F*. The serial changes in the RS-T segment in V_3 and V_4, together with the presence of a constant QRS pattern, were indicative of pericarditis. The pathologic findings, as pointed out above, consisted of marked left ventricular hypertrophy, right ventricular dilatation and acute epicarditis, and subepicardial myocarditis. There was no evidence of infarction of the septum or anterior wall.

Bizarre QRS Patterns in Leads From the Transitional Zone. In taking the six precordial leads, the electrode is customarily moved from points over the right ventricle to points over the left ventricle. If the electrode happens to cross the septum when shifted from one chest position to the next, an abrupt change from an rS pattern, representing the potential variations of the right ventricle (Lead V_4 of figure 1, *A*), to an Rs deflection, representing the potential variations of the left ventricle (Lead V_5 of fig. 1, *A*), is recorded.* On the other hand, if the electrode happens to straddle the anterior terminus of the septum in one or more leads, transitional complexes, representing varying mixtures of right and left ventricular effects, are recorded. The usual finding at the transitional zone is a QRS complex of relatively low voltage, consisting of R and S deflections that are intermediate in amplitude between those in adjacent leads to the right and left, as exemplified by V_3 of figure 1, *B*. These intermediate complexes often exhibit coarse slurring or notching, as in Lead V_4 of figure 1, *C* and V_3 of figure 1, *H*. Through determination of temporal relationships of such notches with the peaks of the R waves in leads to the right and left,[14] these notches may be recognized as manifestations of the transitional zone and not an indication of an interventricular conduction defect. For example, the notch at the nadir of the S wave in Lead V_3 of figure 1, *H* is synchronous with the peak of the R wave in Lead V_4 and thus marks the arrival of the impulse of the epicardial surface of the anterior apical wall of the left ventricle. In a few cases of left ventricular hypertrophy, bizarre QRS patterns, characterized either by a multiphasic complex or by an initial downstroke, may be found at the transitional zone and may be mistaken for patterns due to myocardial infarction unless analyzed in reference to the findings in adjacent leads.

Multiphasic QRS Complexes at the Transitional Zone: From a hasty glance at figure 1, *F*, one might suspect a localized conduction defect in the anterolateral wall of the left ventricle from the quadriphasic rsR′s′ complex in V_5, as compared with the smooth, unnotched rS and Rs deflections in V_4 and V_6, respectively.

* The lower case letter is used to indicate a relatively small deflection, the upper case letter to indicate a relatively large deflection.

The fact that the QRS interval, as measured in V_5, was similar to that in V_4 is against such an interpretation. Furthermore, the peak of the initial R wave in V_5 was synchronous with the R wave of right ventricular origin in Lead V_3, whereas the peak of the R′ deflection in V_5 was synchronous with the R wave of left ventricular origin in V_6. Hence, Lead V_5 was a transitional lead registering separately the intrinsicoid deflections from the anterior walls of both ventricles. Multiphasic QRS complexes of low voltage in the transitional zone are more difficult to analyze and may require additional leads.

Prominent Q Wave at the Transitional Zone: Q waves in the precordial leads that measure 0.03 second or more from onset to nadir and exceed 25 per cent of the amplitude of the subsequent R wave are ordinarily the result of myocardial infarction, but occasionally may occur in leads at the transitional zone in the absence of infarction. The diagnostic difficulties under these circumstances are exemplified by Cases 11 and 12.

Patient 11, a man 60 years of age, came to the Outpatient Department in June, 1947, with symptoms referable to carcinoma of the stomach. The first electrocardiogram, made on June 27 and reproduced in figure 3, *A*, showed sinus rhythm interrupted by frequent premature auricular beats. The QRS-T pattern in the limb leads and in V_5 and V_6 was considered normal. In Leads V_1 and V_2, a minute initial R wave could be made out, followed by a deep S wave. This small initial R wave disappeared from V_3 and V_4, and a QS deflection was recorded in the former, a triphasic QRS complex in the latter. The triphasic QRS deflection in Lead V_4 began with a downstroke, which ranged from 2 mm. to 5 mm. in depth and from 33 per cent to 200 per cent of the succeeding R wave. The change from an rS deflection in V_2 to a QS in V_3 and the abnormal QR ratio in every cycle of V_4 pointed strongly towards anteroseptal infarction, whereas the contour of the RS-T complexes indicated that infarction, if present, was old and healed. However, an unequivocal diagnosis of anteroseptal infarction was not justifiable from the precordial electrocardiogram for the following reasons: (1) the time from onset to nadir of the Q wave in V_4 was only 0.02 second; (2) Q waves were not detected in V_5 and V_6, as would have been expected if an infarct had been responsible for the relatively deep Q waves in V_3 and V_4; (3) the Q waves were confined to leads that were transitional in type, as indicated by: (a) the low voltage of the QRS in V_3, and V_4, as compared to V_2 and V_5; (b) marked respiratory fluctuations in the depth of the Q wave and the QR ratio in Lead V_4.

During the course of preparation for operation, the tracing was repeated to further investigate the significance of the findings in V_3, and V_4. No essential change was found in the QRS-T pattern of Leads V_1, V_2, V_5, and V_6. In Lead V_3 there was a much larger S wave, comparable in voltage to the S wave of V_1, and V_2. A small initial R was consistently present in Lead V_3, but showed respiratory fluctuations in amplitude. The findings in Lead V_3 on July 22 indicated that this lead reflected chiefly the potential variations of the right ventricle, rather than the transitional zone. Lead V_4 displayed a prominent initial R wave and a tall upright T wave, similar to those in V_5, and V_6, indicating that the electrode had crossed the septum and reflected the potential variations of the anteroapical wall of the left ventricle. The negative findings in leads immediately to the right and left of the septum in this tracing constituted further evidence signifying that the pattern in V_3 and V_4 of the first tracing was representative of transitional zonal effects, rather than anteroseptal infarction. The patient died postoperatively and autopsy revealed a heart of normal weight with a widely dilated coronary tree and no evidence of myocardial infarction. There was moderate right ventricular dilatation, which may have represented a postoperative complication.

Restudy, after the autopsy, of the tracing of June 27 uncovered the following additional data that might account for the unusual normal variations found in Leads V_3 and V_4. The QRS interval measured 0.08 second in V_1 and V_2, 0.07 second in V_3 and V_4 and 0.06 second in V_5 and V_6. This difference in time interval indicated that the forces responsible for the initial R in V_1 and V_2 were not represented in the

remaining leads. The R wave in leads facing the right ventricle and atrium is generally derived in part from the septum and in part from the free wall of the right ventricle. Activation of the septum usually results in transmission of positive potentials to the right precordium and negative potentials to the left precordium, either because of earlier arrival of the impulse in the left side of the septum or greater magnitude of forces developed in the left than in the right half of the septum. A comparison of the initial R waves in right precordial leads showed that it was largest in V_1, the lead furthest removed from the septum, and decreased as the electrode approached the septum. This relationship, together with the absence of a Q counterpart in Leads V_5 and V_6, was strongly against a septal origin for the R wave in V_1 and V_2. On the other hand, the diminishing R wave in the first three leads was compatible with a right ventricular origin, since activation of the relatively thick base of the right venticle near the tricuspid orifice should produce greater electromotive force than activation of the relatively thin apex of the right ventricle. If depolarization of the two sides of the septum began simultaneously and produced forces of approximately equal magnitude, one might expect precordial transmission of negative potentials from the endocardial surface as a consequence of extinction of positive potentials in the center of the septum. The findings in Leads V_3 and V_4 can be accounted for by this hypothesis, assuming that the electrode was situated just to the right of the septum at V_3 and straddled the septum at V_4. The downstroke in Lead V_3 was probably initiated by negative potentials reaching the right ventricular cavity from activation of the right side of the septum and continued by left ventricular cavity potentials transmitted to the right after depolarization of the septum. The initial downstroke in Lead V_4 was probably derived from the right side of the septum in the same manner as the first part of the QS in V_3, whereas the succeeding R wave was undoubtedly due to activation of the anteroseptal wall of the left ventricle, as shown by the synchrony of the intrinsicoid deflection with that in V_5. The origin of the triphasic QRS complex in Lead V_4 of the tracing of June 27 was thus analogous to the origin of the quadriphasic QRS in Lead V_5 in Case 6, figure 1, *F*.

The tracings reproduced in figure 3, *B* were obtained from Patient 12, a 46 year old man, who gave a history of shortness of breath on exertion since April, 1944, and sudden paroxysmal nocturnal dyspnea on July 15, followed by progressive dependent edema. He denied the presence of chest pain. Physical examination revealed signs of rheumatic aortic stenosis and insufficiency complicated by marked congestive failure. The patient was partially digitalized during the last three days in July and received an additional 4½ grains during the three-day interim between the two tracings.

Sinus rhythm was present on August 1, except for two late ventricular premature beats of the fusion type in Lead III. Leads V_5, V_6, and I showed a minute Q wave, tall slurred upstroke, slightly delayed intrinsicoid deflection, slightly depressed RS-T junction, and diphasic T wave, typical of left ventricular hypertrophy. The deep S wave in V_1, which extended below the lower edge of the record, was consistent with left ventricular hypertrophy, but the initial R was unusually large, measuring 0.8 to 1.0 millivolts, and raised the question of coexistent right ventricular hypertrophy. Some cycles of Lead V_2 were similar to those of V_1; others displayed a minute Q, followed by a slightly smaller R, but a comparable S wave. A minute Q wave was consistently present in Lead V_3 and was followed by a much smaller upstroke, ranging from 1 to 3 mm. in amplitude. Lead V_4 showed marked fluctuations in the QRS contour, despite a uniform P-R interval and a regular ventricular rhythm. These fluctuations were present during quiet breathing, but were markedly accentuated by deep breathing, which was in progress while the strip dated August 1 was made. The variability of the QRS pattern in V_4 indicated that the electrode was at the transitional zone and was attributed to respiratory shifting in cardiac position. Nevertheless, the prominent notched Q wave present in every cycle of V_4 was interpreted as evidence of anteroseptal infarction, because of consistent prolongation in time interval from its onset to nadir and because of an habitually abnormal

Q-R ratio. The diagnosis of anteroseptal infarction was strongly supported by elevation of the RS-T junction in V_3 and V_4. The RS-T displacement in these leads could not have been a transitional phenomenon, since the RS-T junction was depressed in leads further to the right and left, whereas the T wave, which was upright and doubled in V_3 and V_4, was inverted to diphasic both in V_1 and in V_5 and V_6. A diagnosis of recent anteroseptal infarction was confirmed by the cove inversion of the T waves in V_3 and V_4, which took place during the next three days. These RS-T changes were believed independent of digitalis, not only because of the small dose administered during interim, but also because of the lack of Q-T shortening. The QRS pattern was essentially the same as in the previous tracing, but the respiratory fluctuations were not as marked in V_4 because of the fact that this tracing was made during quiet breathing.

The patient returned to the hospital on September 17, 1944, with congestive failure. An electrocardiogram made the day following admission showed no significant change in QRS pattern, except a T-wave evolution consistent with the healing of an infarction. Death occurred on September 20, 1944, and autopsy revealed a 637-gram heart, showing marked left and moderate right ventricular hypertrophy associated with rheumatic aortic stenosis. The coronary tree injected well and showed no narrowing or occlusion. The heart was opened by the Schlesinger technique and no evidence of infarction was found on gross inspection. Seven microscopic blocks were taken from the anteroseptal wall of the left ventricle, extending from apex to base, and showed no myocardial lesion apart from hypertrophy and slight perivascular fibrosis consistent with his old rheumatic infection. Similar negative findings were observed in the posterior wall, but unfortunately no blocks were taken from the lateral wall of the left ventricle. Discard of the gross specimen has made further pathologic study impossible.

Proceeding upon the assumption that an infarct had not been overlooked pathologically, one might be tempted to explain the QRS pattern in V_3 and V_4 as a transitional zonal phenomenon analogous to that already discussed in connection with Case 11. However, the serial changes in RS-T complex could not be accounted for in this manner. Although the RS-T evolution was compatible with a localized area of acute pericarditis or subepicardial myocarditis, no traces were found at autopsy. Thus, we were dissatisfied with the hypothesis that the abnormal Q waves in V_3 and V_4, fulfilling the criteria for infarction, represented a rare variant of the transitional zone, whereas the RS-T evolution in the same leads was due to a localized, pathologically undetectable pericarditis. This made it necessary to reconsider the alternative possibility that an infarct was present in August, 1944, but was missed at autopsy seven weeks later. Complete healing during the interim cannot account for the discrepancy between the electrocardiographic and pathologic findings because the Q-wave abnormalities were still present in a tracing obtained two days before death. Experience during the past four years with other cases, particularly Case 144 of a previous report,[7] has suggested a better explanation. The electrocardiogram in Case 144 revealed abnormal Q patterns in V_3 and V_4, but not in V_5 and V_6, whereas autopsy disclosed an infarct localized to the lateral wall of the left ventricle. The potential variations of the epicardial surface of this lateral infarct were transmitted to the precordium, rather than to the axilla, because of marked counterclockwise rotation of the heart. Since a comparable degree of counterclockwise rotation was present in Patient 12 of this series, it seems most likely that a lateral infarct was responsible for the QRS-T abnormalities in V_3 and V_4, but was missed at autopsy because of failure to take sections from the lateral wall.

Midprecordial Leads with Bizarre RS-T Patterns Suggestive of Infarction. These may be encountered as a result of: (1) displacement of the transitional zone for the T wave to the right of that for the QRS; (2) registration at the transitional zone of an intermediate RS-T complex, consisting of an RS-T segment resembling that in leads to the right and a T wave like that in leads to the left.

The deeply inverted T wave in Lead V_3 of Patient 7, figure 1, *G*, in association with an

almost equiphasic RS deflection of transitional type, might raise the question of a marginal zone of subepicardial infarction. Its close resemblance to the T wave in left ventricular lead V_4 suggested that the T wave in V_3 was chiefly left ventricular in origin and, like that in V_4, could have been due to uncomplicated left ventricular hypertrophy. Autopsy confirmed the latter and excluded infarction. The fact that the transitional zone for the T wave was located to the right of that for the QRS may have been due to counterclockwise rotation of the heart during mechanical systole, which begins during the registration of the intrinsicoid deflection.

The inscription of an elevated RS-T segment like that in leads further to the right, followed by sharp inversion of the T wave like that in leads to the left, may produce an effect simulating the cove negative T wave of recent myocardial infarction. This was observed in Patient 47, as a manifestation of the transitional zone in uncomplicated left ventricular hypertrophy and in Patient 31 with uncomplicated left bundle branch block, and will be reported in future communications.

Summary

QRS-T patterns in Wilson precordial leads that may be mistaken for patterns due to myocardial infarction include those of left ventricular hypertrophy and dilatation; right ventricular hypertrophy and dilatation; left bundle branch block; right bundle branch block; alterations in blood potassium; myocardial ischemia; pericarditis and subepicardial myocarditis; and certain arrhythmias. To bring out the differential diagnosis, cases have been selected for presentation in which myocardial infarction was diagnosed, or at least considered in the electrocardiographic interpretation during life, but was subsequently excluded by meticulous postmortem examination. The electrocardiographic differentiation of myocardial infarction from left ventricular hypertrophy is considered in this article and the differentiation from the remaining lesions will form the subject of future reports.

The electrocardiograms of 12 patients, in whom autopsy revealed either left ventricular hypertrophy or a normal myocardium and excluded the possibility of myocardial infarction, have been presented because of one or more of the following signs suggestive of myocardial infarction:

A. Unusual depth of the Q waves customarily recorded in leads from the left axilla in the presence of left ventricular hypertrophy or greater voltage of the Q wave in Lead V_4 than in V_5 or V_6.

B. RS-T patterns in leads from the left precordium or axilla, characterized by either: (1) sharp inversion of the T wave, accompanied by a slightly elevated or isoelectric RS-T junction, instead of the customary slight depression; (2) marked RS-T depression; (3) deeper inversion of the T wave in Lead V_4 than in V_5 or V_6; (4) rapid changes in serial tracings.

C. QS deflections in Leads V_1 and V_2.

D. Abnormal elevation of the RS-T junction in leads from the right side of the precordium.

E. Bizarre QRS patterns in leads from the transitional zone, characterized by either: (1) a multiphasic complex, (2) an abnormal initial downstroke.

F. Abnormal displacement of the RS-T segment and/or inversion of the T wave in leads from the transitional zone.

The correlation of electrocardiographic and pathologic findings and the differentiation from the pattern of myocardial infarction are brought out through a detailed analysis of each electrocardiogram.

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QRS-T Patterns in Multiple Precordial Leads that May Be Mistaken for Myocardial Infarction

II. Right Ventricular Hypertrophy and Dilatation

By Gordon B. Myers, M.D.

The electrocardiograms of patients with pathologic evidence of right ventricular hypertrophy and/or dilatation and exclusion of myocardial infarction are presented to bring out certain features likely to be mistaken for myocardial infarction: (1) abnormal qR or QS patterns or cove plane inversion of the T waves in leads from the right precordium; (2) reduction in the amplitude of the initial R wave or replacement by a QS deflection and/or change from an upright to an inverted T wave as the electrode is moved from the V_1 position to the transitional zone; (3) abnormal qrS deflections in leads from the left axilla.

DETAILED descriptions have been published of the Wilson precordial electrocardiogram in right ventricular hypertrophy and dilatation,[1–5] and in anteroseptal infarction, [1, 6–11] but little attention has been devoted to the differentiation of these two conditions. The precordial leads in uncomplicated right ventricular hypertrophy and/or dilatation often show abnormalities that resemble the pattern associated with infarction of the septum and/or anterior wall of the left ventricle. To bring out the differential diagnosis, 15 previously unreported cases have been selected because of (1) findings in the precordial leads likely to be mistaken for myocardial infarction, (2) postmortem demonstration of right ventricular hypertrophy and/or dilatation and pathologic exclusion of myocardial infarction. The method of electrocardiographic and pathologic study is similar to that employed in the preceding study.[12]

I. Right Ventricular Hypertrophy

In right ventricular hypertrophy, leads from the right precordium may display one of the following signs[1–3]: (A) right bundle branch block; (B) a diagnostic pattern appearing in Lead V_{3R}, usually in V_1, and occasionally in V_2, characterized by (1) a QRS of normal duration, (2) a prominent late upstroke, usually preceded by either a relatively small q wave or by a minute r and narrow s, resulting in a qR or rsR′ configuration, * (3) a delayed intrinsicoid deflection that terminates at the isoelectric line or is followed by an abnormally small s (or s′) wave, (4) depression of the RS-T junction, and (5) inversion of the T wave; (C) evidence suggesting dilatation of the right ventricle, but not hypertrophy; (D) an electrocardiogram showing no abnormality. In this section, it is our purpose to present cases of right ventricular hypertrophy with more or less diagnostic patterns in V_{3R}, V_1, and/or aV_R to bring out certain features that may be mistaken for those of myocardial infarction. Cases without diagnostic signs of right ventricular hypertrophy in precordial leads, but with changes referable to right ventricular dilatation, will be presented in Section II. Right bundle branch block will be deferred until the next communication.

Electrocardiographic patterns referable to right ventricular hypertrophy may present certain features that might be mistaken for those of myocardial infarction, namely: (A) the qR deflection in right precordial leads may be abnormally broad, suggesting right bundle branch block, due to septal infarction; (B)

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* The lower case letter is used to indicate a relatively small deflection; the upper case letter, to indicate a relatively large deflection.

the Q wave in right precordial leads may be unusually deep in proportion to the succeeding R, resulting in abnormal ratios in the range customarily associated with myocardial infarc- leads at the transitional zone, either finding suggesting anteroseptal infarction; (F) the normal Q wave may persist in left ventricular leads, accompanied by marked reduction in the

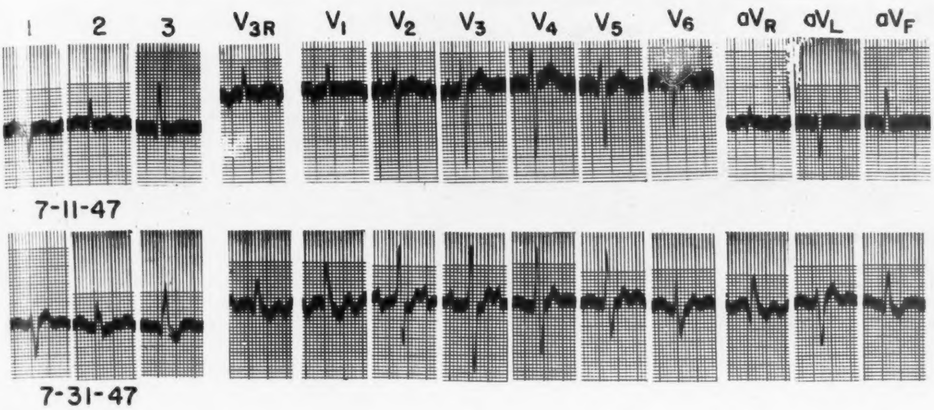

FIG. 1.–Serial electrocardiograms in Case 13

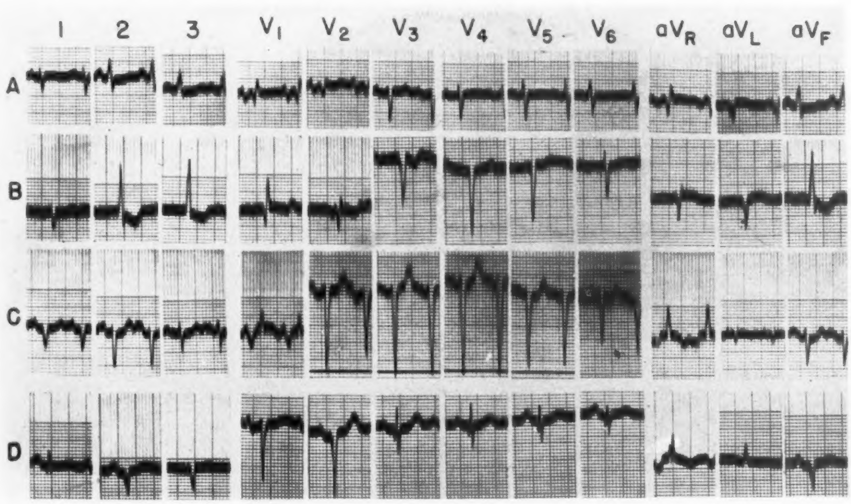

FIG. 2.–Electrocardiographic findings in right ventricular hypertrophy. *A*, Case 14; *B*, Case 15; *C*, Case 16; *D*, Case 17.

tion; (C) sharp inversion of the T wave without the usual RS-T depression may occur in leads from the right precordium, and may resemble the "coronary" T wave; (D) localized reduction in the amplitude of the R wave, or (E) replacement by a QS deflection, may occur in R and exaggeration in the S wave secondary to right ventricular hypertrophy, thus producing a pattern suggestive of anterolateral infarction. These features are collectively illustrated by the electrocardiograms of Cases 13 to 17, inclusive, reproduced in figures 1 and 2.

A. *Abnormally Broad qR Deflection in Right Precordial Leads.* As exemplified by the tracing of July 31, 1947, in figure 1, abnormally broad qR deflections in right precordial leads brings up the question of right bundle branch block, due to infarction of the septum. Both electrocardiograms in figure 1 were obtained from Patient 13, a boy aged 13 years, who was admitted to the hospital with congestive failure associated with rheumatic mitral stenosis and insufficiency complicated by a recent right subclavian thrombophlebitis and pulmonary infarction. Despite maintenance of prothrombin concentration between 20 per cent and 30 per cent, the thrombophlebitis extended into the right jugular, the innominate, and left subclavian veins, and repeated pulmonary emboli occurred, resulting in increasing right ventricular dilatation and failure.

The tracing of July 11, obtained upon admission, was considered diagnostic of right ventricular hypertrophy,[3] because of (1) an abnormally large R wave in Leads V_{3R} and V_1 with small antecedent Q wave in the former lead, but without succeeding S wave in either lead; (2) a time interval from beginning of the QRS complex to the onset of the intrinsicoid deflection that was abnormally long in V_{3R} and V_1 and greater than in V_5, and V_6; (3) a prominent S wave in Leads V_5 and V_6.*

*Since this conclusion was reached, Kossmann and associates[4] have advanced a different interpretation based on new evidence, which must be reviewed and reevaluated. These workers took leads around the circumference of the chest and from within the right ventricular cavity in patients with clinical or pathologic evidence of right ventricular hypertrophy and found patterns in the customary precordial leads similar to that in the tracing of July 11 in Case 13. The qR pattern of Leads V_1 and V_{3R} was demonstrated over the entire right side of the chest as far posteriorly as the V_{8R} position, whereas the rS pattern of V_6 was distributed over the entire left side of the chest from the V_2 to the V_8 position. They contended that (1) the rS pattern was transmitted from the right ventricle because of its presence in Leads V_2 through V_4, which were anatomically over the right ventricle; (2) the qR pattern in all leads from the right side of the chest was transmitted from the left ventricle because of their observation that the hypertrophied right ventricle does not become as thick as the normal left ventricle and thus would not be expected to give rise to an R wave that is greater in amplitude and longer in duration than the normal R from the left ventricle.

In an effort at an anatomic rationalization of their premise of predominant transmission of the potential variations of the left ventricle to the entire right side of the chest, Kossmann and associates postulated an extreme degree of clockwise rotation. Sufficient cardiac rotation to permit transmission of the potential variations of the posterobasal wall of the left ventricle to the right arm and thereby produce a prominent late R wave in Lead aV_R is a common observation both in normal individuals and in patients with isolated left ventricular hypertrophy. On the other hand, sufficient cardiac rotation to permit transmission of the potential variations of the posterobasal wall of the left ventricle to the right precordium and thereby produce a prominent late R wave in V_{3R} and V_1, like that in figure 1, has not been encountered in any of our patients proved to have a normal heart or preponderant left ventricular hypertrophy at autopsy. All of our patients with such findings in V_{3R} and V_1, who have come to autopsy, have had definite evidence of right ventricular hypertrophy. If the positive potentials responsible for the late upstroke in V_{3R} and V_1 of Patient 13 had been transmitted from the posterobasal wall of the left rather than from the right ventricle, a relatively larger R wave would have been expected in Lead aV_R. The fact that the R waves in V_1 and V_{3R} were much greater than the R wave in aV_R, both in absolute voltage and in relative amplitude in respect to the antecedent Q wave, was in keeping with a right ventricular origin, but was strongly against a left ventricular source.

It would appear that the studies of Kossmann and associates, made with simultaneous leads from the right ventricular cavity and precordium in another case of right ventricular hypertrophy, provide a more satisfactory explanation for the registration of a prominent late R wave in leads to the right of the midline and an rS complex in leads to the left. They found an rsR′r″ complex in V_2, and V_1 and an rsR′ complex in Leads V_{3R} to V_{5R} and demonstrated conclusively that the R′ deflection, which was comparable in amplitude to the R wave in Lead V_{3R} of our Patient 13, was produced by activation of the free wall of the right ventricle. They postulated that the late R wave was derived from the base of the hypertrophied right ventricle, which at autopsy is often thick and solid, in contrast to the apex, which is thin and trabecular. This may well account for the registration of a prominent late R wave in Leads V_1 and V_{3R}, facing the thickened base of the hypertrophied right ventricle in Patient 13, and for the registration of an rS deflection in Leads V_2, V_3, and V_4 over the relatively thin apex of the hypertrophied right ventricle. They also demonstrated that the minute initial r wave in leads from the right precordium was produced by septal activation and the

Comparison of the electrocardiogram obtained on July 31, one day before death, with that taken on admission revealed a length-

ening of the QRS interval from 0.09 to 0.12 second without significant change in the relative amplitudes of the component phases of the QRS in the limb leads or in Leads V_{3R} and V_1. In the remaining precordial leads, the R wave increased at the expense of the S. If the tracing of July 31, 1947, were examined without benefit of history or without access to previous electrocardiographic studies, the possibility of right bundle branch block due to septal infarction would demand serious consideration. The broad, slurred Q wave and late peak of the R wave in V_{3R} and V_1 were comparable to the findings in patients with pathologically proved septal infarction.[11] The depression of the RS-T junction and straightening of the RS-T segment were atypical of infarction, but could be attributed to digitalization. However, in the clinical appraisal of this patient, no consideration was given to the possibility of septal infarction because of the history and previous electrocardiographic findings.

The question arose as to whether the terminal lengthening in time of the QRS interval was due to right bundle branch block or to a conduction defect in the free wall of the right ventricle. The possibility of uncomplicated right bundle branch block was practically excluded by the Q waves in V_{3R} and V_1, since activation of the entire septum from left to right should have produced sufficient electromotive force to have led to the registration of an initial R wave in these leads. Delay in arrival of the impulse at the base of the dilated right ventricle presumably permitted registration of a Q wave in V_{3R} and V_1, whereas slowing in the passage of the impulse through the hypertrophied ring of muscle near the tricuspid orifice probably accounted for the prolonged slurred R wave in the same leads. The increased amplitude and duration of the R wave in leads from the left precordium may have been due to a lesser degree of prolongation in activation of the thinner apical portion of the right ventricle.

The heart weighed 357 grams and showed marked right ventricular hypertrophy, as evidenced by a ratio of 1.1:1.0.[13] The basal portion of the right ventricular wall measured 1.1 cm. in thickness, whereas the anteroapical one-third of the left ventricular wall measured 1.2 cm. in thickness. There was a marked rheumatic mitral stenosis, admitting only the tip of one finger. The coronary tree was widely dilated and there was no evidence of myocardial infarction. There were multiple pulmonary infarcts of various ages, involving the greater portion of both lungs.

Upon reanalysis of the electrocardiograms in the light of the pathologic findings and the observations of Kossmann, it was concluded that the prominent late R waves in Leads V_{3R} and V_1 of the first tracing were a manifestation of right ventricular hypertrophy and that the increased amplitude and duration of the Q and R waves in the same leads in the final tracing were referable to a conduction defect in the free wall of the dilated and hypertrophied right ventricle. A right bundle branch block with loss of the customary initial R wave was considered unlikely in view of the hypertrophy of the septum and dilatation of the right ventricle.

B. *QR Complex of Normal Duration with Relatively Deep Q Wave in Right Precordial Leads.* This finding, resulting in abnormal ratios in the range customarily associated with myocardial infarction, may occur in association with right ventricular hypertrophy, as exemplified by Patients 14 and 15, whose electrocardiograms are reproduced in figure 2, *A* and

intervening S was produced by negative potentials from the left ventricular cavity, transmitted during the interim between completion of septal activation and arrival of the impulse in the free wall of the right ventricle. In more distant leads, such as V_{6R} to V_{8R}, the initial r wave disappeared. The left ventricular forces responsible for the R in V_6 produced a Q wave in V_{6R} and the activation of the outer wall of the right ventricle resulted in the late R wave of V_{6R}, completing a qR complex, analogous to that in Lead V_{3R} of our Patient 13. In patients with a qR complex in V_{3R} and V_1, associated with right ventricular hypertrophy, the question remains as to whether the minute initial r, due to early positivity of the right ventricular cavity, is lost in transmission to the precordium or whether the right ventricular cavity is initially negative, due to reversal in the direction of mean electrical forces associated with activation of an hypertrophied septum. Simultaneous right ventricular cavity and precordial leads will be needed to settle this question.

B. The QRS interval was normal in both cases, measuring 0.09 second in the former and 0.08 second in the latter. Lead V_1 of figure 2, *A* displayed an initial downstroke, 3 mm. in depth and 0.03 second in duration, followed by an upstroke extending 3.5 mm. above the isoelectric line and attaining a peak at the end of 0.06 second. Lead V_2 also showed an equiphasic QR complex, lower in voltage, but comparable in time relationships to the QR deflection of V_1. In Lead V_1 of figure 2, *B* there was a Q wave 4 mm. in depth and 0.02 second in duration, followed by an R wave extending 8 mm. above the isoelectric line and attaining a peak 0.05 second after the onset of the QRS complex. The QR deflection in Lead V_2 consisted of a downstroke 5 mm. deep and an upstroke of 3 millimeters.

If QR patterns, like those in V_1 and V_2 of figure 2, *A* and *B* were recorded in leads facing the epicardial surface of the left ventricle, a diagnosis of infarction of the subendocardial layer of the subjacent left ventricular wall would be justified. However, the V_1 and V_2 positions were over the right atrium in Patient 14, as evidenced by the diphasic P waves with steep intrinsicoid downstroke, and were apparently in the vicinity of the right atrium in Patient 15, as indicated by the fact that distinct f waves of auricular fibrillation were made out in V_1, V_2, and V_3, but not in precordial leads further to the left or in the limb leads.

In the antemortem interpretation of both tracings, the prominent late R waves in V_1 and V_2 were believed to have been derived from the basal portion of the right ventricle and were taken as evidence of right ventricular hypertrophy. Since then, Kossmann and associates[4] have advanced the opinion that the qR deflections registered in leads from the right side of the chest in cases of right ventricular hypertrophy are transmitted from the posterobasal wall of the left ventricle to the right atrium, whereas the rS deflections recorded in leads from the entire left side of the chest are transmitted from the right ventricle. This necessitated a reanalysis of our cases in the light of their interpretations.

If the potential variations of the posterobasal wall of the left ventricle had carried through to the right precordium to produce the late R wave in V_1, one would have expected better transmission to the right arm and a relatively larger R wave in Lead aV_R. The fact that the late R wave in V_1 of figure 2, *B* was much greater than that in aV_R, both in actual amplitude and in relative amplitude, was in keeping with a right ventricular origin, but was strongly against a left ventricular source. On the other hand, the similarity of the QR patterns in Leads V_1 and aV_R of figure 2, *A* did not permit conclusions as to their source and necessitated utilization of other evidence. This was obtained through a comparison of the QRS patterns in the first two with those in the last four precordial leads. The minute initial R and prominent S waves in V_3 were evidently transitional and the findings in V_1, V_2, and those in V_4 through V_6 were thus transmitted from opposite ventricles. The progressive increase in the R at the expense of the S deflection as the electrode was moved from the V_4 to the V_6 position was compatible with transmission from the anterolateral wall of the left ventricle, but not from the apex of the right ventricle. The comparative QRS patterns in the last four precordial leads constituted strong indirect evidence, signifying that the QR complexes in V_1 and V_2 were derived chiefly from the right ventricle. Hence, reanalysis of these electrocardiograms in the light of the evidence brought forward by Kossmann and associates confirmed the original conclusion, namely, that the findings in V_1 and V_2 of both cases were referable to right ventricular hypertrophy.

Patient 14 was a 29 year old housewife, who gave a history of rheumatic heart disease since the age of 15 years and congestive heart failure of three months' duration, precipitated by pregnancy. The electrocardiogram in figure 2, *A* was taken on admission, while the patient was in advanced congestive failure, but after partial digitalization. Death occurred two weeks later, as a result of pulmonary infarction, and autopsy revealed fish-mouth mitral stenosis with marked right ventricular hypertrophy, the right ventricle equaling the left in weight. There was no evidence of myocardial infarction.

Patient 15 was a 52 year old man, who had had rheumatic heart disease since the age of

21 years and was admitted to the hospital with acute congestive failure secondary to lobar pneumonia. The electrocardiogram reproduced in figure 2, *B* was obtained after the administration of 0.8 mg. of Cedilanid. Death occurred four days later and autopsy revealed a 478-gram heart with fish-mouth mitral stenosis and marked right ventricular hypertrophy. The basal portion of the right ventricular wall measured 1.3 cm. in thickness, whereas the apical portion of the left ventricular wall measured 1.4 cm. in thickness. There was no evidence of myocardial infarction. It was, therefore, concluded that the abnormal QR patterns in Leads V_1 and V_2 of this and the preceding patient were due to right ventricular hypertrophy.

C. *Sharp Inversion of the T Wave without the Customary RS-T Depression in Leads From the Right Precordium.* This finding may occur in association with right ventricular dilatation and hypertrophy and the pattern may resemble the "coronary" T wave. This is exemplified by Lead V_1 of Patient 16, figure 2, *C*. This patient was a 25 year old man, who gave a history of rheumatic heart disease since the age of 19 years and was admitted to the hospital because of sudden severe orthopnea and pleural pain referable to pulmonary infarction.

The electrocardiogram was obtained on admission before the administration of cardiac glycosides. The terminal portion of the inverted T wave of V_1 was interrupted by a large diphasic P wave. The broad slurred postintrinsicoid negative phase of this P wave was ascribed to left auricular hypertrophy. The QRS interval was 0.08 second. Careful scrutiny of Lead V_1 revealed an rsR′ complex of the type previously attributed to incomplete right bundle branch block.[3] However, as Kossmann and associates[4] have pointed out, the brief duration of the initial R wave was compatible with normal septal activation and militated against a conduction defect in the septum. The prominent late R′ deflection was attributed to activation of the hypertrophied free wall of the right ventricle[4] and was indicative of right ventricular hypertrophy. It is noteworthy that the minute initial R wave of V_1 could not be made out in Lead V_{3R}. This lead displayed merely a qR complex comparable to the sR′ deflection of V_1. The slight elevation of the RS-T junction in V_1 and the sharp inversion of the T wave resulted in a pattern suggestive of the "coronary" T wave. However, sharp inversion of the T wave of this degree may be associated with right ventricular hypertrophy, particularly when accompanied by acute right ventricular dilatation, as in acute pulmonary embolism. The elevation, rather than the customary slight depression of the junction following the rsR′ complex in V_1, was unusual in right ventricular hypertrophy, but could be explained by superimposition of a prominent upright auricular T wave. The latter would have been expected after the deep, broad negative phase of the P wave.

Death occurred on the third hospital day from infarction of both lower lobes and autopsy revealed a fish-mouth mitral valve. The right ventricle was markedly hypertrophied and almost equaled the left ventricle in weight and thickness. The base of the right ventricle was 1.2 cm. in thickness, whereas the anteroapical wall of the left ventricle was 1.4 cm. in thickness. There was no evidence of myocardial infarction. Thus, the rsR′ complex and the sharply inverted T wave of Lead V_1 were referable to right ventricular hypertrophy.

D. *Localized Reduction in the Amplitude of the R Wave at the Transitional Zone.* This is a common finding in uncomplicated right ventricular hypertrophy and must be differentiated from localized reduction in the amplitude of the R wave in a left ventricular lead occurring as a residue of healed anteroseptal infarction.[1, 7]

The initial R wave in Lead V_3 in Case 14, figure 2, *A*, was reduced below 1 mm., but was readily recognized as a manifestation of the transitional zone by comparison with patterns in leads to the right and left. In the presence of definite signs of right ventricular hypertrophy in V_1 or in both V_1, and V_2, no significance should be attached to localized reduction in the amplitude of the R wave in a lead further to the left unless one can be certain that the electrode is well beyond the transitional zone and over the anterolateral wall of the left ventricle.

E. *QS Deflection in Leads at the Transitional Zone.* This may occur in association with uncomplicated right ventricular hypertrophy and

may be mistakenly interpreted as due to anteroseptal infarction. The diagnostic difficulties are exemplified by Leads V_3 and V_4 in Case 15, figure 2, *B*. These leads displayed a QS deflection containing an R equivalent in the form of slurring located near the beginning of the downstroke. These findings would have been interpreted as evidence of old anteroseptal infarction, if a normal rS deflection had been present in right ventricular Leads V_1 and V_2 or if an abnormal Q wave had been recorded in left ventricular Lead V_6. The QS deflections in V_3 and V_4 and the minute R wave and early notch on the downstroke of the S wave in V_5 were considered a transitional zonal effect because of the prominent late R wave referable to right ventricular hypertrophy in Leads V_1 and V_2 and because of the distinct initial upstroke in V_6, the first lead distinctly to the left of the transitional zone. In patients with right ventricular enlargement, the pathway of the electrode is often parallel to the long axis of the septum, and the electrode may lie directly over the anterior terminus of the septum in positions V_2, V_3, and/or V_4. The QS complex occasionally recorded in such leads in the absence of infarction probably represents cavity potentials, transmitted because of cancellation of opposing vectors, derived from septal activation by impulses proceeding from its two endocardial surfaces.

The clockwise rotation commonly associated with right ventricular dilatation and hypertrophy facilitates transmission of the potential variations of the transitional zone or right ventricle to the left arm. The QS deflection in Lead aV_L was attributed to transmission of the potential variations of the transitional zone rather than to lateral infarction in the antemortem interpretation, but high precordial and axillary leads should have been taken for more definite exclusion of the latter.

The foregoing electrocardiographic analysis was confirmed at autopsy, which, as already described, revealed fish-mouth mitral stenosis, marked right ventricular hypertrophy, and no evidence of infarction. A number of microscopic blocks were made in order positively to exclude the presence of infarction.

F. *Persistence of the Normal Q Wave in Left Ventricular Leads Accompanied by Marked Reduction in the R and Exaggeration of the S Wave.* This condition, when secondary to right ventricular hypertrophy, may result in a precordial electrocardiogram that may be readily mistaken as representative of anterolateral infarction. This is illustrated by figure 2, *D*, reproducing the electrocardiogram in Case 17. The patient was a woman, 74 years of age, with a marked pigeon-breast deformity. She was hospitalized because of strangulated hernia and was studied electrocardiographically during convalescence from an exteriorization of the gangrenous bowel together with ileostomy.

In Lead V_1, a normal rS complex was recorded; in Lead V_2, a QS deflection, containing an R equivalent in the form of a small early notch; and in V_3, V_4, V_5, and V_6, a triphasic QRS was registered. The last four leads displayed a Q wave of constant depth and duration (2 mm. in amplitude and 0.02 second from onset to nadir), an R wave which decreased in height as the electrode was moved to the left, and a prominent S wave throughout. This latter finding, together with the large R wave in Lead aV_R, raised the question of right ventricular hypertrophy and led to the taking of Lead V_{3R}. This lead showed an rS complex like that in V_1, and thus failed to support the suspicion of right ventricular hypertrophy. An antemortem diagnosis of old healed anterolateral infarction was accordingly made because of the QS deflection in V_2 and the abnormal QR ratio in V_3 through V_6 in the presence of a normal rS complex in V_{3R} and V_1. The notched QS deflection in Lead aV_F was interpreted as evidence of continuation of the infarct into the posteroapical wall of the left ventricle.

Death occurred four weeks after admission following a second operation, and autopsy revealed chronic cor pulmonale with moderate right ventricular hypertrophy, as evidenced by a ratio of 1.2 and a right ventricular thickness of 1.0 centimeter. No evidence of infarction was found on careful gross examination or in multiple microscopic blocks.

Upon reconsideration of the electrocardiogram in the light of the pathologic findings, it would appear that more significance should have been placed on the prominent double-

peaked R wave in Lead aV_R. The fact that the ventricular complex in aV_R began with an upstroke rather than a Q wave indicated transmission from the right rather than the posterobasal wall of the left ventricle. The double-peaked R of right ventricular origin in aV_R thus contrasted sharply with the qR deflection of left ventricular origin in aV_L. The initial upstroke in aV_R was probably due to passage of the impulse through the septum, the second upstroke to activation of the hypertrophied free wall of the base of the right ventricle. An attempt to trace the source of the QRS pattern in aV_R would probably have led to the correct antemortem diagnosis and should have been made in this case because of the chest deformity and the discrepancy between the findings in aV_R and V_{3R}. The fact that the Q wave in left ventricular Leads V_3 through V_6 was normal in duration, constant both in size and duration, and essentially the reciprocal of the initial R wave in V_1 and aV_R should have led to the suspicion that it was a normal manifestation of septal activation rather than a result of infarction. The notched QS in V_2 was evidently a manifestation of the transitional zone between the anterior walls of the right and left ventricles, whereas the notched QS in Lead aV_F was apparently due to predominant transmission of the potential variations of the posteroseptal region to the left leg.

II. Right Ventricular Dilatation

The electrocardiographic diagnosis of right ventricular dilatation is difficult in the absence of classic signs of associated hypertrophy. Findings referable to right ventricular dilatation are likely to be mistaken for those of anteroseptal myocardial infarction. One reason for the confusion is that Leads V_1, V_2, and V_3 may reflect the potential variations of the free wall of the right ventricle, the right side of the septum, and, to a variable extent, the anterior wall of the left ventricle. Acute right ventricular dilatation may be manifested by striking, though not pathognomonic, changes in the RS-T segments and T waves in Leads V_1, V_2, and V_3, which resemble those found in the same leads in the presence of acute infarction of the anteroseptal wall of the left ventricle.

Another reason for the confusion is that enlargement of the right ventricle, together with the usually associated dilatation of the right atrium and clockwise rotation of the heart, facilitates the predominant transmission of the potential variations of the apical portion of the right ventricle as far to the left as the midclavicular line, sometimes to the anterior axillary line, and occasionally even to the midaxillary line. Furthermore, the transitional zone is not only displaced to the left into Leads V_4, V_5, and/or V_6, but is likely to be broad, probably owing to a shift in the long axis of the septum to a plane more nearly parallel with the pathway of the electrode. The anatomic relationship of the heart to fixed points on the chest wall is further altered when the right ventricular dilatation is associated with pulmonary emphysema and lowering of the diaphragms. Under the foregoing circumstances, errors may be made if one fails to recognize that the patterns in leads from the left precordium are transmitted predominantly from the right ventricle and interprets the findings as if the patterns had been derived from the left ventricle.

The electrocardiographic features of right ventricular dilatation that might be mistaken for those of myocardial infarction include: (A) sharp inversion of the T waves with elevated or isoelectric RS-T junctions in the first three or four precordial leads; (B) rapid changes in the direction and amplitude of the T waves of right precordial leads in serial tracings; (C) QS patterns in the first three or more precordial leads; (D) localized reduction in the amplitude of the initial R wave as the electrode is moved leftward from the V_1, and V_2 positions, particularly when accompanied by a change from an upright to an inverted T wave; (E) progressive diminution of the initial R wave as the electrode is moved leftward from the V_1, and V_2 positions into the transitional zone, particularly when accompanied by change from upright to inverted T waves; (F) replacement of the initial R wave by a QS deflection or W-shaped complex in leads near the transitional zone, particularly when accompanied by inversion of the T wave. These features are collectively illustrated by the electrocardiograms in Cases 18 to 27, inclusive, reproduced in figures 3, 4, and 5.

A. *Sharp Inversion of the T Wave with or without Elevation of the RS-T Segment in the First Three or Four Precordial Leads.* This may occur as a manifestation of acute right ventricular dilatation[14-18] and may resemble the RS-T changes associated with recent anteroseptal infarction. It is illustrated by the electrocardiograms reproduced in figure 3, obtained in Cases 18 to 21, inclusive.

Patient 18 was a woman, aged 68 years, who was admitted because of a senile psychosis. Bilateral femoral phlebothrombosis developed in the hospital and was complicated by repeated pulmonary embolism. The electrocardiogram reproduced in figure 3, *A* was obtained after the development of pulmonary infarction, but before the administration of digitalis. The first three precordial leads showed elevation of the RS-T junction and inversion of the terminal portion of the T wave. Anteroseptal infarction was excluded as a cause of the T-wave inversion in these leads because of (1) the presence of upright T waves in Leads V_4, and V_5 nearer the anteroseptal wall of the left ventricle, (2) the presence of an initial upstroke in all precordial leads, and (3) a progressive increase in the amplitude of the R wave as the electrode was moved to the left. These features, together with the displacement of the transitional zone to the left, led to an electrocardiographic diagnosis of acute right ventricular dilatation.

The patient died of pulmonary embolism three and one-half weeks after admission. There was marked dilatation of the right ventricle and atrium and moderate right ventricular hypertrophy, as indicated by a ratio of 1.1 associated with a cardiac weight of 338 grams. There was mild coronary sclerosis without narrowing or evidence of infarction. The electrocardiographic findings were believed referable to right ventricular dilatation and failed to disclose the hypertrophy also found at autopsy.

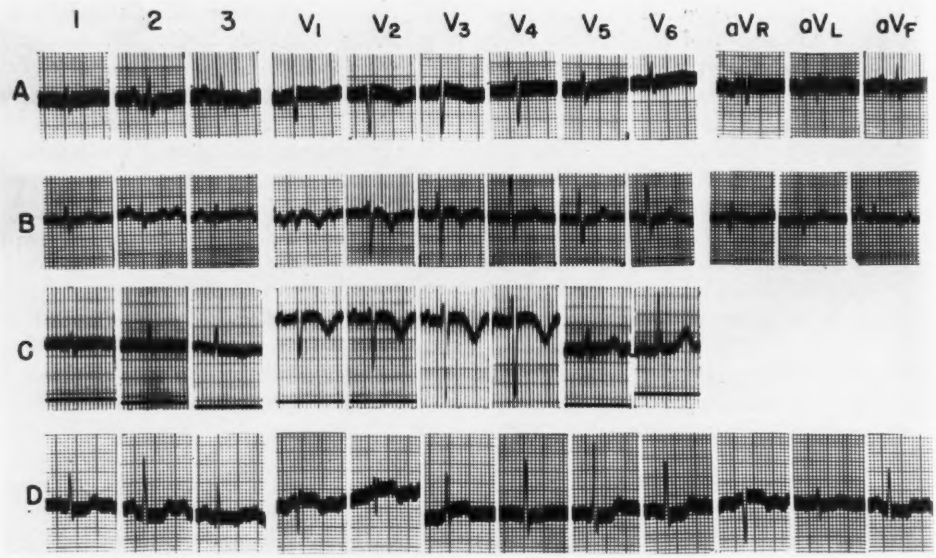

FIG. 3.–Electrocardiographic findings in right ventricular dilatation. *A*, Case 18; *B*, Case 19; *C*, Case 20; *D*, Case 21.

The electrocardiogram reproduced in figure 3, *B* was obtained from Patient 19 prior to the administration of digitalis. This patient, a housewife aged 47 years, gave a history of pollen asthma since childhood and increasing exertional dyspnea for several years and was admitted to the hospital with left ventricular failure complicated by miliary tuberculosis.

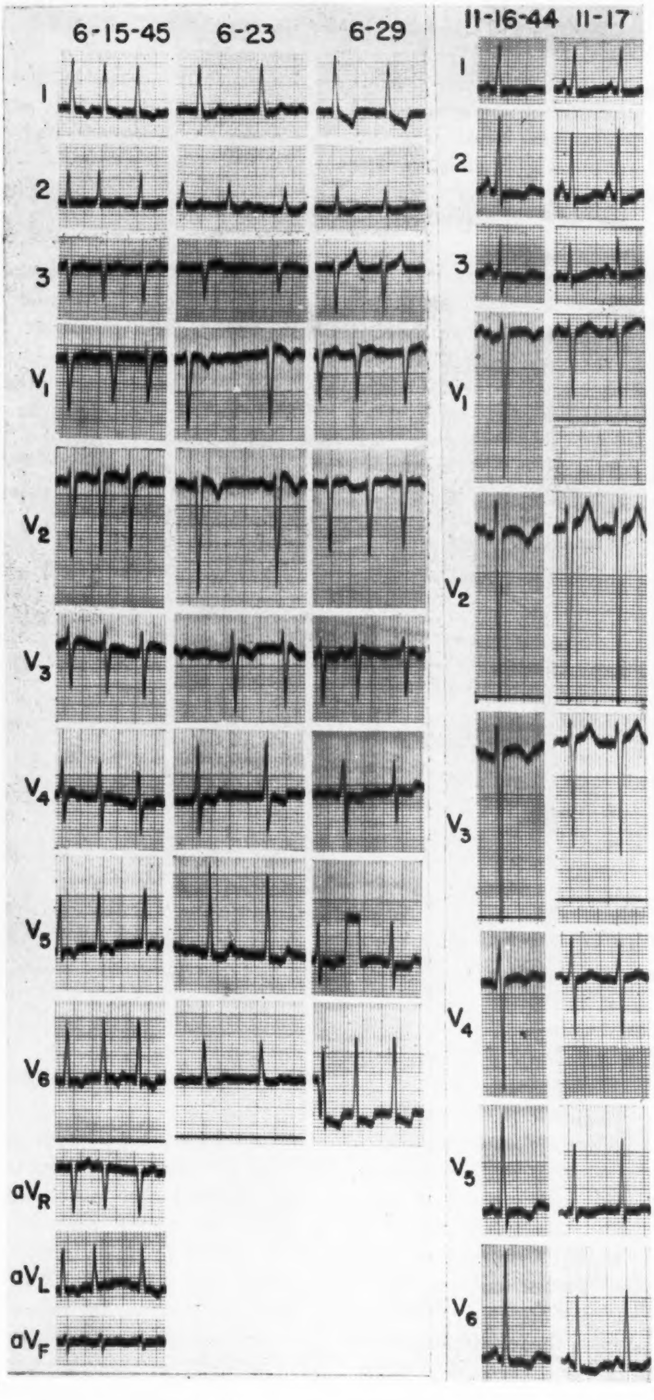

FIG. 4.-Serial changes in acute right ventricular dilatation. *A*, Case 22; *B*, Case 23.

The striking features of the electrocardiogram consisted in upward bowing of the RST-segments and sharp inversion of the T waves in Leads V_1, V_2, and V_3. Despite the covelike contour of the T waves, the findings could be ascribed to acute cor pulmonale rather than anteroseptal infarction because of (1) the normal upright T wave in V_4, the first lead to the left of the transitional zone; (2) the absence of Q waves from V_1 to V_4 and the progressive increase in the R waves of these leads; (3) the doubling of the initial R wave in Leads V_2 and V_3 near the transitional zone (indicating right and left ventricular derivation). Although the contour of the T waves in the first three precordial leads was consistent with pericarditis, the limitation of the inverted T waves to leads over the right ventricle excluded the possibility of a diffuse subepicardial lesion. The slight elevation of the RS-T junction in Lead V_1 was believed due to an upright T_a wave.

The patient died from the combined effects of left ventricular failure and miliary tuberculosis on the day after the electrocardiogram was made. The heart weighed 460 grams, the increase being due chiefly to left ventricular hypertrophy of hypertensive origin. There was slight hypertrophy and marked dilatation of the right ventricle and atrium, due in part to chronic pulmonary emphysema, in part to recent passive congestion. The miliary tuberculosis did not involve the heart and there was no evidence of pericarditis, subepicardial myocarditis, infarction, or coronary narrowing. The T-wave abnormalities were thus referable to right ventricular dilatation.

The electrocardiogram reproduced in figure 3, *C* was obtained from Patient 20, a man aged 59 years, hospitalized because of carcinoma of the cecum and thrombophlebitis of the right femoral vein, complicated by repeated pulmonary embolism. No cardiac glycosides were given. The tracing is presented because of the deeply inverted T waves in Leads V_1 through V_4, resembling those associated with organizing myocardial infarction. However, the electrocardiographic findings were attributed to acute cor pulmonale for essentially the same reasons as in the two preceding cases, namely: (1) the limitation of the inverted T waves to right ventricular leads, (2) the normal initial R waves in these leads.

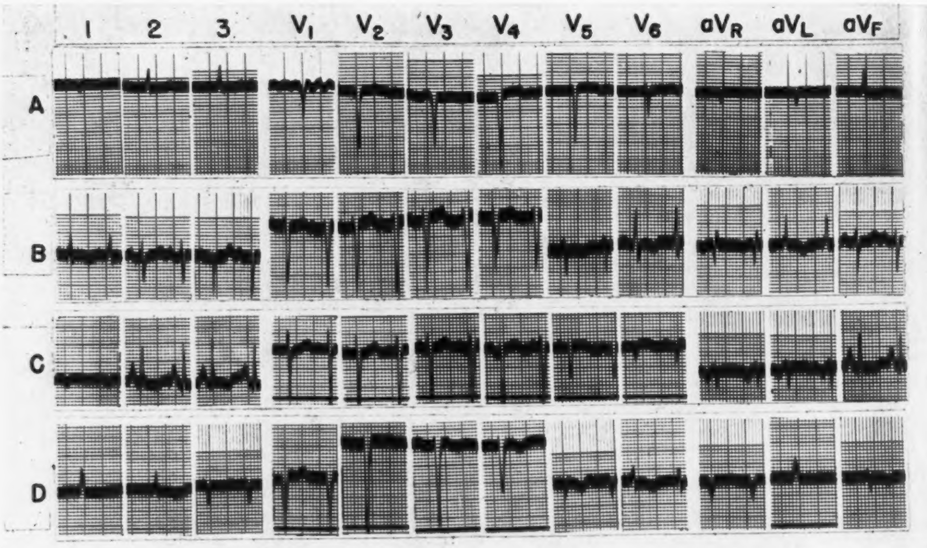

FIG. 5.–Electrocardiographic findings in right ventricular dilatation. *A*. Case 24; *B*, Case 25; *C*, Case 26; *D*, Case 27.

Death occurred three weeks after the tracings were made from carcinomatous perforation of the cecum and autopsy revealed multiple pulmonary infarcts. The heart weighed 375 grams and showed dilatation of the right ventricle and atrium without hypertrophy. The coronary vessels were moderately sclerotic, but patent throughout. Epicardium and myocardium appeared normal on gross and histologic examination.

Patient 21 was a man, aged 73 years, admitted to the hospital because of a perforated peptic ulcer. Convalescence was uneventful until the ninth postoperative day, when he had a sudden attack of dyspnea and weakness. The electrocardiogram reproduced in Fig. 3, *D* was obtained two hours later, while the patient was in shock. No cardiac glycosides had been given.

Leads V_1 and V_2 displayed an rSr′ complex, indicating that the electrode faced the epicardial surface of the right ventricle, whereas Lead V_3 showed an Rs deflection, signifying that the electrode had crossed the transitional zone. Slurring was present near the end of the intrinsicoid deflection in V_3 and was simultaneous with the R′ deflection of V_1 and V_2, but later than the peak of the R in left ventricular leads V_4, V_5, and V_6. Incomplete right bundle branch block was excluded as a possible cause of the pattern in V_1 and V_2 because of the brevity of the initial R wave. The r′ deflection in these leads was not derived from the posterobasal wall of the left ventricle because of the absence of a larger late upstroke from Lead aV_R. Activation of the conus pulmonalis was believed responsible for the r′ deflection in V_1 and V_2 and the simultaneous slurring of the descending limb of the R wave in V_3.

A more striking feature of the tracing was the RS-T pattern, characterized by elevation and upward convexity of the RS-T segment and terminal inversion of the T wave in Leads V_1, V_2, V_3, and aV_R and by depressed segments and upright T waves in V_5, V_6, and aV_F. Three possibilities were considered: (1) acute myocardial infarction reaching the epicardium in the anteroseptal aspect of the left ventricle and confined to the subendocardial layer in the anterolateral and posterior aspects; (2) recent infarction localized to the anteroseptal aspect of the left ventricle with reciprocal RS-T depression in lateral and posterior leads; (3) acute cor pulmonale with ischemia of the anterolateral and posterior walls of the left ventricle, secondary to shock. The preservation of the initial R wave in all precordial leads was against infarction, but did not exclude the possibility of a very recent lesion. On the other hand, the early transition and the RS-T elevation in left ventricular Lead V_3 were against cor pulmonale, but did not exclude it because Lead V_3 also apparently reflected potential variations of the nearby conus pulmonalis. A positive differentiation, therefore, could not be made from this electrocardiogram.

The patient made a complete symptomatic recovery by the next day and had no further complaints until the thirteenth postoperative day, when a second attack occurred, terminating fatally within fifteen minutes. Autopsy revealed a massive terminal and previous smaller pulmonary emboli. The heart weighed 440 grams and showed right ventricular dilatation and hypertrophy. There was minimal coronary sclerosis, but no narrowing and no evidence of myocardial infarction or pericarditis. The RS-T elevation in V_1, V_2, and V_3 and aV_R was, therefore, a manifestation of acute cor pulmonale. The RS-T depression in V_5, V_6, and aV_F may have been reciprocal to the elevation in right precordial leads, but was more likely due to acute left ventricular ischemia secondary to shock.

B. *Rapid Changes in the Inverted T Waves of Right Precordial Leads in Serial Tracings.* These changes also occur in association with acute cor pulmonale [14–18] and may be mistaken for those due to recent myocardial infarction. The problem in diagnosis is illustrated by figure 4, which represents the electrocardiograms in Cases 22 and 23, respectively.

Patient 22 was an obese woman, aged 54 years, who gave a history of hypertension of two years' duration and increasing congestive failure for three weeks. Auricular fibrillation was consistently present. The electrocardiogram of June 15, 1945, figure 4, *A*, was obtained on the first hospital day after the administration of 0.8 mg. Cedilanid. Leads V_5 and V_6 displayed prominent late R waves,

slightly depressed RS-T junctions, and sharply inverted T waves compatible with the presence of left ventricular hypertrophy. The T wave was upright and of normal contour in right ventricular leads V_1, V_2, and V_3 and the RS-T junction was isoelectric in V_1 and elevated 1.0 mm. in V_2 and V_3. Slight inversion of the T wave was present in transitional lead V_4.

A second tracing made the following day after full digitalization, but not reproduced in figure 4, showed the classic straightening of the RS-T segments, but no change in the direction of the T waves. A constant maintenance dose of $1\frac{1}{2}$ grains digitalis daily was given for the remainder of her hospital stay.

The course was uneventful until June 21, when she was suddenly seized with dyspnea and stabbing pain in the right side of the chest. Repeat electrocardiogram on June 23 showed striking changes in the RS-T complexes, particularly in right precordial leads. The RS-T junction in V_1 had become elevated and the T wave sharply inverted; the RS-T junction in V_2 showed increased upward displacement and the T wave had also become sharply inverted. Although these RS-T changes resembled those associated with acute anteroseptal infarction, they were definitely attributed to acute cor pulmonale because (1) the RS-T elevation and T-wave inversion were more marked in Leads V_1 and V_2 over the right ventricle than in Leads V_3 and V_4 over the transitional zone and anterior wall of the left ventricle, (2) the absence of reduction or obliteration of the normal initial R waves in the first four precordial leads. It is noteworthy that the terminal portion of the T wave had become upright in the last three precordial leads, thereby maintaining its reciprocal relationships with the T waves in right precordial leads.

The patient was symptom free on June 29 and the electrocardiogram had returned to the original configuration. The rapid change from sharply inverted to upright T waves in Leads V_1 and V_2 together with the decrease in upward displacement of the RS-T junctions was typical of the evolution accompanying recovery from acute cor pulmonale.

The patient had a second attack of abrupt dyspnea and pleural pain on July 1 and died suddenly on July 8, 1945. Death was due to pulmonary embolism and autopsy revealed organizing pulmonary infarcts. The heart weighed 729 grams and showed marked left ventricular hypertrophy and right ventricular dilatation, but no evidence of myocardial infarction or pericarditis.

Patient 23 was a man, aged 47 years, who gave a history of exertional dyspnea for eleven months and paroxysmal nocturnal dyspnea for three months. He was admitted to the hospital during an exceptionally severe attack of acute pulmonary edema.

The electrocardiogram of November 16, 1944, figure 4, *B*, was obtained soon after admission, following the administration of 3 grains of digitalis leaf. Leads V_5 and V_6 displayed large R waves, slightly delayed intrinsicoid deflections, and diphasic to inverted T waves indicative of left ventricular hypertrophy. The deep broad S waves in right ventricular leads V_1, V_2, V_3, and V_4 were compatible with left ventricular hypertrophy, but the slightly elevated RS-T junctions and cove negative T waves in the same leads could not be explained in this manner.

The RS-T pattern in the first four precordial leads raised the question of recent anteroseptal infarction, ischemia of the anteroseptal wall of the left ventricle, acute pericarditis, and acute right ventricular dilatation. The possibility of acute anteroseptal infarction was virtually excluded by the normal initial R waves in the first four precordial leads. Ischemia of the anteroseptal wall of the left ventricle was regarded as an unlikely factor because of (1) the absence of RS-T depression and (2) the greater depth of the T wave in V_2 than in leads nearer the anteroseptal wall of the left ventricle (V_3, and V_4). The possibility of pericarditis as a cause of the inverted T waves in the first four precordial leads was practically excluded by their replacement by upright T waves of normal contour on the following day. On the other hand, the rapid evolution was consistent with acute cor pulmonale and could be correlated with marked clinical improvement and disappearance of pulmonary edema under therapy, which included $4\frac{1}{2}$ grains of additional digitalis. The RS-T changes

in V_5, and V_6 could be explained by digitalis effect.

The patient died of "malignant" hypertension two months after the tracings of November 16 were made. The heart weighed 672 grams and showed marked left ventricular hypertrophy, but no evidence of infarction or pericarditis. The coronary tree was patent throughout and of normal caliber. There was no evidence of pulmonary infarction. In view of the clinical findings during the first two hospital days together with the subsequent autopsy findings, it was concluded that the RS-T patterns in Leads V_1, V_2, V_3, and V_4 on November 16 were due to acute right ventricular dilatation secondary to extensive pulmonary congestion and edema from acute left ventricular failure.

C. *QS Pattern in the First Three or More Precordial Leads.* This may occur in association with right ventricular dilatation, with or without accompanying hypertrophy. Zuckermann and associates[5] studied 50 cases of chronic cor pulmonale without clinical signs of myocardial infarction and found either a QS complex, a W-shaped QRS, or a deep Q wave in right precordial leads of 36 per cent of the series. Nevertheless, when a QS deflection is recorded in the first three or more precordial leads, the possibility of anterior infarction extending into the septum[11] must be given serious consideration and a study of additional leads must be made for differentiation from right ventricular dilatation, and from the rare normal variant associated with marked clockwise rotation and/or displacement of the heart to the left.

The problem in differential diagnosis afforded by QS deflections in the first five precordial leads is illustrated by figure 5, *A*. This electrocardiogram was obtained from a 45 year old man (Patient 24) soon after admission to the hospital with advanced congestive failure and following partial digitalization. Auricular fibrillation was present and was manifested by course f waves in V_1, varying fine to moderately coarse f waves in V_2, and V_3, and no undulations in the remaining precordial leads or in any of the limb leads. This suggested that the electrode was in the vicinity of the right atrium at position V_1 and probably also at V_2 and V_3. The precordial leads in this tracing did not cover a sufficiently wide area to provide adequate exploration of both the right and left ventricles, as shown by the lack of contrasting patterns in the leads at either end (V_1 and V_6 positions). In fact, the change from a QS in V_5 to an rS deflection in V_6 suggested that the electrode was approaching the transitional zone and that Leads V_4 and V_5, as well as V_1, V_2, and V_3, reflected the potential variations of the right side of the septum and epicardial surface of the right ventricle. The absence of a Q wave preceding the upstroke in transitional lead V_6 was against infarction continuing from the septum into the anterior wall of the left ventricle.

The question remained as to whether the QS deflection in the first five precordial leads was due to healed infarction confined to the septum or merely to right ventricular dilatation. To settle this question, a repeat electrocardiogram, including leads to the right of the V_1 position and beyond the V_6 position, was necessary. This was obtained after restoration of compensation, and still showed auricular fibrillation with prominent f waves confined to Leads V_{3R} and V_1. These two leads displayed a QS deflection; V_2, V_3, and V_4 showed an rS complex, the initial upstroke increasing from 1 mm. in V_2 to 3 mm. in V_4; Lead V_5 exhibited an equiphasic RS deflection of transitional origin and Lead V_6 showed a prominent late R wave suggesting left ventricular hypertrophy.

The second electrocardiogram thus revealed no evidence of infarction and consequently ruled out septal infarction as a cause of the QS deflections in the first tracing. Although it was impossible positively to exclude an erroneously high position of the electrode[4] or an abundant application of electrode jelly over the entire pathway of the electrode[19] as an explanation for these QS deflections, the findings could be adequately accounted for on the assumption of a technically accurate tracing. Thus, the registration of prominent f waves as far as the V_3 position, QS deflections as far as the V_5 position, and the transitional zone beyond midaxilla in the first tracing, was compatible with marked dilatation of the right atrium and ventricle, and marked clockwise rotation associated with advanced congestive failure. The subsequent limitation of f and QS waves to the V_{3R}

and V_1 positions and shift of transitional zone to the anterior axillary line in the second tracing, made after restoration of compensation, was compatible with reduction in distention of the right atrium and ventricle and decrease in the degree of clockwise rotation.

The patient died, on the twenty-second hospital day, of intercurrent pneumonia. Autopsy revealed a 566-gram heart, with left ventricular hypertrophy associated with rheumatic mitral insufficiency and hypertension and accompanied by marked right ventricular dilatation. There was no evidence of myocardial infarction. The necropsy findings thus supported the above antemortem interpretation of the electrocardiograms.

D. *Localized Reduction in the Amplitude of the Initial R Wave in a Lead to the Left of V_1 or V_2.* This may occur in association with right ventricular dilatation, but may raise the question of anteroseptal infarction, particularly when accompanied by change from an upright to an inverted T wave. This is exemplified by figure 5, *B*, obtained from Patient 25, a hypertensive man, aged 55 years, who was admitted to the hospital with advanced congestive failure complicated by bronchopneumonia. No cardiac glycosides were given.

The inversion of the T wave in left ventricular leads V_6 and aV_L and the slight slurring and prolongation of the ascending limb of the R wave in aV_L suggested left ventricular hypertrophy. Small r and relatively deep S waves were recorded in the first five precordial leads. The initial R wave measured 1.0 mm. in V_1, 1.5 mm. in V_2, 2.5 mm. in V_3, then decreased to 1.5 mm. in V_4 and became slurred and 2.0 mm. in amplitude in V_5. The localized decrease in the amplitude of the R wave in V_4 and V_5 might raise the question of anteroseptal infarction, but the accompanying diminution in voltage of the S wave and slurring of the QRS complex suggested that it constituted a manifestation of the transitional zone. The change from an upright T wave with concave RS-T segment in V_1, V_2, V_3, and V_4 to an inverted T wave with convex RS-T segment in V_5 might also raise the question of anteroseptal infarction. However, the resemblance of the T wave in V_5 to that in V_6 suggested that it, too, was a manifestation of left ventricular hypertrophy. The findings in V_5 could be explained by the assumption that (1) the electrode faced the right ventricular side of the septum during the registration of the QRS, (2) the heart rotated sufficiently during systole so that the electrode faced the left ventricular side of the septum during registration of the T wave. A diagnosis was therefore made of left ventricular hypertrophy and right ventricular dilatation with displacement of the transitional zone to the anterior axillary line.

Death, due to congestive failure and bronchopneumonia, occurred nine hours after admission to the hospital. The heart weighed 490 grams and showed left ventricular hypertrophy, due to hypertension, and acute right ventricular dilatation. The coronary vessels were patent and there was no evidence of infarction. The postmortem findings thus confirmed the electrocardiographic interpretation.

E. *Progressive Diminution of the Initial R Wave, Accompanied by Change From an Upright to an Inverted T Wave.* As the electrode is moved from the V_1 or V_2 positions towards the left, progressive diminution of the initial R wave, accompanied by change from an upright to an inverted T wave, may occur in association with right ventricular dilatation, but may be easily mistaken as representative of anterior myocardial infarction, as exemplified by figure 5, *C*. This electrocardiogram was obtained from a 66 year old man (patient 26) soon after admission to the hospital and before the administration of cardiac glycosides.

An rS complex was recorded in all six precordial leads and was of normal voltage in V_1, V_2, V_3, and V_4, was reduced by half in V_5, and again cut in half in V_6. The initial R wave measured 5 mm. in V_1 and decreased by approximately 1 mm. in each successive lead up to V_6, where it was barely perceptible. The T wave in the first four precordial leads was upright and was accompanied by a normal, upwardly concave RS-T segment in V_1, V_2, and V_3 and a convex segment in V_4. The elevated, convex RS-T segments and the inversion of the terminal portion of the T waves in Leads V_5 and V_6 were abnormal and, along with the marked reduction of the initial R wave, strongly suggested a patchy acute anterolateral infarction. However, the alternative possibility of marked right ventricular dilata-

tion with transitional zonal effects in V_5 and V_6 had to be considered because of (1) the presence of rS patterns in all six precordial leads and (2) the reduced voltage and slurring to notching of the S wave in V_5 and V_6.

To settle the diagnosis, it was necessary to take sufficient leads to the right of position V_1 and beyond position V_6 until contrasting QRS patterns were recorded at the two extremes. An rS deflection like that in V_1 and V_2 was recorded in V_E and V_{3R}, V_{4R}, and V_{5R}, indicating transmission of the potential variations of the right ventricle to the right anterior chest. Lead V_7 displayed an Rs complex, consisting of a brief initial upstroke 5 mm. high followed by a barely perceptible S wave, isoelectric RS-T junction, and inverted T wave; Lead V_8 exhibited a small monophasic R wave and similar RS-T complex. These findings signified that the potential variations of the left ventricle were referred to the left side of the back. The absence of a Q wave from V_7 and V_8 was strongly against myocardial infarction as the cause of the findings in Leads V_5 and V_6. The low voltage and slurring of the QRS in these two leads indicated that the electrode was in the vicinity of the transitional zone. The rough correspondence of the RS ratio in V_5 and V_6 to that in leads further to the right suggested that the electrode lay to the right of the septum during ventricular activation, whereas the inversion of the terminal portion of the T wave, like that in V_7, suggested that the heart had rotated sufficiently during systcle so that the left ventricle faced towards the anterior axilla.

After study of the additional leads, a diagnosis of right ventricular dilatation was made and the abnormal QRS-T patterns in V_5 and V_6 were ascribed to the transitional zone. This diagnosis was in accord with the clinical findings. The patient gave a history of asthma for thirty years and a chronic productive cough for five years. Physical examination showed clubbing, barrel chest, and obstructive pulmonary emphysema.

Death occurred on the tenth hospital day. Autopsy revealed chronic bronchitis, obstructive pulmonary emphysema, but no evidence of myocardial infarction. The heart weighed 327 grams and the right atrium and ventricle were dilated. Relative right ventricular hypertrophy was present, as indicated by a ratio of 1.2 and by comparison of the thickness of the two ventricles. The right ventricle measured 1.2 cm. at the base and 0.8 cm. at the apex; the apical third of the left ventricle measured 1.3 cm. anteriorly and 1.8 cm. laterally. The progressive decrease in the amplitude of the R wave as the electrode was moved from position V_1 in the vicinity of the tricuspid ring to position V_4, which was presumably near the apex of the right ventricle, could be correlated with the progressive decrease in thickness of the right ventricular wall from base to apex. Although the size and thickness of the right ventricle in this patient closely approached that in Patient 16, classical electrocardiographic signs of right ventricular hypertrophy were not found in this patient, but were present in Patient 16.

F. *Replacement of the Initial R by a QS Deflection or W-Shaped Complex Accompanied by Change from an Upright to an Inverted T Wave.* This may occur in association with right ventricular dilatation, as the electrode is moved from the V_1 or V_2 positions toward the left, and may lead to an erroneous diagnosis of myocardial infarction, as in Patient 27, whose electrocardiogram is reproduced in figure 5, *D*. This patient was a man, aged 78 years, who had a barrel chest secondary to obstructive pulmonary emphysema and had been under treatment for hypertensive heart disease for several years. He was admitted to the hospital with marked congestive failure after neglecting to take digitalis for six weeks.

The electrocardiogram was obtained after the administration of 0.8 mg. Cedilanid. Auricular fibrillation was present and the ventricular rate was approximately 110 per minute. The similarity of the rS complexes in the first three precordial leads indicated that the electrode in all three positions faced the epicardial surface of the right ventricle. The depth and the breadth of the S wave in these leads were suggestive of left ventricular hypertrophy. The reduction in amplitude and slurring of the S wave in V_4 suggested that the electrode was approaching the transitional zone, but the general correspondence of the RS ratio to that in V_1, V_2, and V_3 indicated that the electrode was still to the right of the septum. The initial R wave failed to show the usual progressive increase in

amplitude in the first four precordial leads, measuring 1.0 mm. in V_1 and V_2 and only 1.5 mm. in V_3 and V_4. More important, however, was the presence of an initial Q wave in V_5 and the reduction of the R wave to a notch on the downstroke of the QS complex. The T waves in V_1 and V_2 were upright and of normal contour, but those in V_3, V_4, and V_5 were inverted and were associated with slightly elevated convex RS-T segments. The T-wave abnormalities in these leads were believed independent of Cedilanid for the following reasons: (1) the contour of the RS-T segment, (2) the relatively long QT interval, (3) the fact that cardiac glycosides tend to make T waves opposite to the main deflection of the QRS. On the basis of the QRS and T abnormalities in V_3, V_4, and V_5, a diagnosis was made of organizing anteroseptal infarction.

In the electrocardiographic interpretation, too little attention was given to the absence of a Q wave from Lead V_6. If an infarct involves enough of thickness of the wall to result in the registration of a notched QS deflection in a given lead, it should extend sufficiently into the subendocardial layer of the surrounding muscle to result in a marginal qR deflection in the next adjacent lead. This discrepancy should have led to repetition of the electrocardiogram, including leads from additional points on the anterolateral aspect of the left side of the chest, but the patient died of pulmonary embolism before this could be undertaken.

Myocardial infarction was not found on careful gross examination and its possibility was definitely excluded by means of multiple microscopic blocks. The coronary arteries were of normal caliber on injection and showed only Grade 1 sclerosis. The heart weighed 553 grams and showed coexistent left ventricular hypertrophy due to hypertension and right ventricular hypertrophy and dilatation, due chiefly to obstructive pulmonary emphysema. Although the right ventricle measured 1.4 cm. in thickness at the base and 0.8 cm. at the apex and the left ventricle, 1.8 cm. in the anterior and 2.5 cm. in the lateral wall, the electrocardiogram failed to show diagnostic signs of either right or left ventricular hypertrophy, perhaps because of the tendency for the effects of the one to neutralize those of the other. In view of the autopsy findings, the notched QS deflection in V_5 was apparently a transitional zonal phenomenon. During the inscription of the QRS, the electrode at position V_5 probably lay over the anterior terminus of the septum and received negative potentials from the ventricular cavities as a consequence of extinction of positive potentials in the center of the septum. The resemblance of the inverted T waves of V_3, V_4, and V_5 to the terminal portion of the inverted T wave of left ventricular lead V_6 suggested that the transitional zone for the T wave was to the right of that for the QRS because of systolic rotation of the heart between inscription of the QRS and T waves.

Summary

In uncomplicated right ventricular hypertrophy and/or dilatation, multiple precordial leads often show abnormalities which resemble those associated with infarction of the septum and/or infarction of the anterior wall of the left ventricle. The differential diagnosis is brought out through the presentation of 15 cases selected because of the presence of (1) electrocardiographic findings originally regarded as indicative or at least suggestive of myocardial infarction, and (2) postmortem demonstration of right ventricular hypertrophy and/or dilatation and pathologic exclusion of myocardial infarction.

In 5 of the cases, the electrocardiogram gave evidence of right ventricular hypertrophy, but exhibited one or more of the following signs likely to be mistaken for those due to myocardial infarction: (A) abnormally broad qR deflection in right precordial leads suggestive of right bundle branch block due to septal infarction; (B) Q wave in right precordial leads that was unusually deep in proportion to the succeeding R wave, resulting in abnormal ratios in the range customarily associated with myocardial infarction; (C) cove plane inversion of the T wave in leads from the right precordium; (D) localized reduction in the amplitude of the R wave or replacement by a QS deflection in leads at the transitional zone, suggesting an-

teroseptal infarction; (E) persistence of the normal Q wave in left ventricular leads accompanied by marked reduction in the R and exaggeration of the S wave, suggesting anterolateral infarction.

In the other 10 cases, the electrocardiogram exhibited one or more of the following signs referable to right ventricular dilatation, but suggestive of myocardial infarction: (A) sharp inversion of the T waves with elevated or isoelectric RS-T junctions in the first three or four precordial leads; (B) rapid changes in the direction and amplitude of the T waves of right precordial leads in serial tracings; (C) QS patterns in the first three or more precordial leads; (D) progressive decrease or localized reduction in the amplitude of the initial R wave as the electrode was moved leftward from the V_1 or V_2 position, accompanied by a change from an upright to an inverted T wave; (E) replacement of the initial R wave by a QS deflection or W-shaped complex in leads near the transitional zone, accompanied by a change from an upright to an inverted T wave.

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The Relationship of Unipolar Chest Leads to the Electrical Field of the Heart

By Robert P. Grant, M.D.

Using a method for measuring the electrical forces of the human heart in three dimensional space, studies of the precordial leads are reported which were designed to determine whether these deflections are principally measurements of the electrical field of the heart as a whole or are dominated by the forces from the region of the heart immediately beneath the electrode. It was found that the former was the case, which leads to a simpler and more rational method for interpreting the electrocardiogram than has been available heretofore.

The interpretation of the QRS and T deflections in the precordial electrocardiogram has been empiric and uncertain because it has not been known to what extent the precordial lead deflections are measurements of the potential variations of the portion of the ventricular myocardium directly beneath the electrode and to what extent they represent the potential variations of the ventricular muscle as a whole. This shortcoming does not exist in interpretation of the limb leads. The limb lead electrodes are so remote electrically from the heart that, in effect, they record the potential variations of the heart as a whole, that is, as if there were single central dipoles for the excitation processes.[1, 2] Because of this, the limb lead deflections can be used to measure the resultant magnitude and direction in the frontal plane of the electrical forces of the heart. This has clarified and simplified interpretation of the limb leads and has led to the development of such useful tools in clinical electrocardiography as the mean electrical axis, instantaneous electrical axes, and the ventricular gradient.

Precordial lead deflections, on the other hand, are recorded from electrode positions so much nearer the center of the electrical field that it has seemed unlikely that the various surfaces of the ventricular myocardium could be electrically equidistant from each of these electrode positions. Therefore, most workers have felt that the mathematical methods so useful in interpretation of the limb leads could not be extended to interpretation of the precordial leads. However, since both limb and precordial leads are semidirect leads, and since there is only a relative difference between them in electrical remoteness from the heart, perhaps there are certain characteristics of the precordial deflections which represent measurements of the electrical forces of the heart as a whole. If these could be demonstrated, the precordial leads could be used to measure the electrical forces of the heart in the anteroposterior plane. By combining the measurements of the forces in this plane with those of the frontal plane made from the limb leads, the characteristics of the forces as they exist in three-dimensional space within the body could be determined. This would make it possible to base the clinical interpretation of the electrocardiogram on the relative magnitudes and directions of the QRS and T electrical forces in space. Such a method for interpreting the electrocardiogram would be much simpler, more rational and more accurate than methods based upon memorizing empirically established deflection sizes and contours on a number of arbitrarily selected leads.

Methods

The purpose of these experiments was to determine the extent to which the deflections recorded from precordial leads are measurements of the mean QRS and T electrical forces of the heart in the human subject. It is neces-

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sary to discuss certain theoretic principles underlying the method chosen for studying the problem before the method is described in detail.

Two principal assumptions were made in selecting the method. It was assumed that body surface deflections were measurements of an electrical field propagated in a volume conductor from central dipoles.[3] This makes it possible to consider the electrical processes of the heart as resultant electrical vectors. A second assumption was that the electrical conductive properties of the human body are reasonably uniform. The uniformity of conductivity in the body has been a point of controversy among students of electrocardiography for many years. Recent theoretic and experimental studies in the human subject leave little doubt, however, that this assumption is reasonably valid.[3, 4]

These premises permit one to apply to the problem of the precordial leads the physical laws governing the distribution of an electrical field arising from a vector at the center of a homogeneous cylindrical volume conductor. In such a field, a plane of zero isopotentiality extends perpendicularly from the center of the vector to the surface of the cylinder, separating the surface into an area of positive potential on one side of this plane and negative potential on the other side. The line of zero isopotentiality defined on the surface of the cylinder where the plane intersects the surface is called the null contour. Its position is determined by the direction but not the magnitude of the vector at the center of the cylinder. It can be calculated for a cylinder, then, if the direction of the vector and the size of the cylinder are known. Or, this calculation can be reversed, and the direction of a vector at the center of a cylindrical volume conductor can be determined if the distribution of positive, negative, and null potentials on the surface of the cylinder are known.

These two concepts, the null contour and the central vector, have counterparts in human electrocardiography and their calculation forms the basis for the present method of studying chest leads. Thus, the null contour of the cylinder is analogous to the pathway of transitional QRS and T complexes (deflections with as much upright as inverted component) around the chest. These transitional pathways can be determined by taking unipolar chest leads from all surfaces of the chest and noting the position on the chest of the electrodes which recorded transitional QRS and T complexes. For the counterpart of the vector at the center of the cylinder, a method is available for calculating the magnitudes and directions of the mean QRS and T electrical forces in three-dimensional space in the human subject with reasonable accuracy.[4] These mean spatial vectors are the average of the vectors generated from the various surfaces of the heart during a single QRS or T cycle. Likewise, for the transitional complex, the chest lead deflections are examined for their resultant or average electrical sign—that is, whether the deflection is principally upright (positive), inverted (negative), or transitional (null) regardless of the overall size of the deflection.

The procedure in these studies, then, was to calculate the mean spatial QRS and T vectors for a given subject. Then, the null contours which these two vectors would project on the surface of a cylinder of the same dimensions as the subject's chest were calculated. These null contours were then compared with the pathways of transitional QRS and T complexes as determined by unipolar leads taken from all surfaces of the chest. If the null contours and transitional pathways coincided on the chest, the chest electrodes could be considered to be recording from the heart as a whole as far as the resultant or net characteristics of the deflection were concerned. In other words, the resultant electrical sign of the chest lead deflections could be considered to be established by single central QRS and T vectors. When the two determinations did not agree, the chest electrodes may have been dominated by the nearest surface of ventricular myocardium and were not recording from the heart as a whole.

To turn to the details of the method used in this study, the calculation of the mean spatial vectors is based on a method first suggested by Wilson, Johnston, and Kossmann[5] which employs the three conventional positions of the limb lead electrodes with a fourth electrode placed on the back directly behind the

heart. These four electrodes form a three-dimensional reference figure electrically. The Einthoven equilateral triangle is converted into an isosceles tetrahedron with the origin or zero-point of the figure at the mid-point of the frontal plane, and the four apices equidistant from this origin. The spatial vectors were calculated from this reference figure as follows: The resultant areas of the QRS and T deflections on the three limb leads were measured and these magnitudes were plotted on the triaxial reference system giving the frontal plane projections of the mean QRS and T vectors.

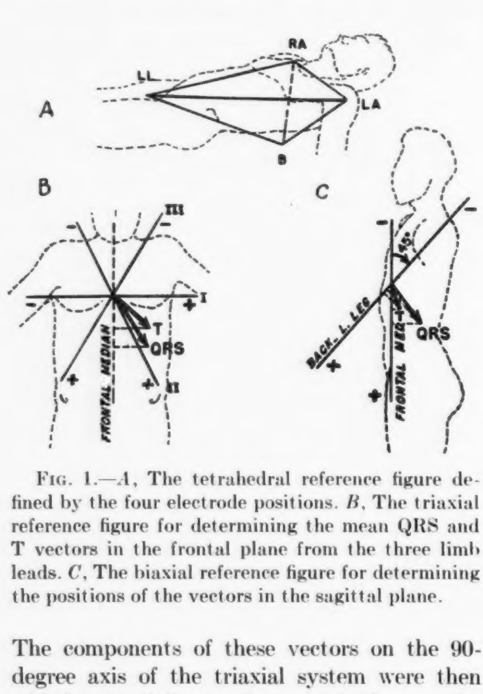

FIG. 1.—*A*, The tetrahedral reference figure defined by the four electrode positions. *B*, The triaxial reference figure for determining the mean QRS and T vectors in the frontal plane from the three limb leads. *C*, The biaxial reference figure for determining the positions of the vectors in the sagittal plane.

The components of these vectors on the 90-degree axis of the triaxial system were then added vectorially to the magnitudes on the back-to-left-leg lead on a 45-degree biaxial system, thus giving the sagittal plane projections of the mean vectors (fig. 1). From the projections of the vectors on these two planes the magnitude and directions of the mean spatial QRS and T vectors can be calculated as described elsewhere.[4]

The QRS and T null contours for a cylinder resembling the subject's chest were next calculated from these mean spatial vectors. The approximate position of a null contour on a subject's chest can be easily visualized if the frontal and sagittal projections of the vector are known. For example, if the vector is found to be directed toward the left leg in the frontal plane, and has a slightly anterior direction in its sagittal projection, the plane perpendicular to this vector can be visualized as intersecting the chest along the upper right region of the chest anteriorly and the lower left region of the chest posteriorly, as shown in figure 2, *A*. If, on the other hand, a vector with this same frontal plane direction should in the sagittal plane prove to be directed somewhat posteriorly, the null contour now lies on the lower left side of the chest anteriorly, and the upper right side of the chest posteriorly, as shown in figure 2, *B*. (In the illustrations, the null contour is drawn as if formed by a plane perpendicular to the vector at its origin instead of at its center; this was done to make the constructions clearer, and is simply an example of vector translation.)

A more precise calculation of the null contour can be performed from the equation:

$$(XE_s\cos\theta) + (YE_f\cos\phi) - (ZE\sin\theta) = 0,$$

where E_s is the magnitude of the projection of the vector on the sagittal plane and θ the angle this projection makes with the antero-posterior axis of the plane, and E_f is the magnitude of the projection of the vector in the frontal plane and ϕ the angle this projection makes with the +90-degree line of the triaxial system (fig. 2, *C*). By making the following substitutions in the equation, four points are located on a cylinder with the same diameters as the subject's chest, and these points define the pathway of the null contour for the cylinder:

Let $X = +a$, $Y = 0$, *and solve for* Z.
Let $X = -a$, $Y = 0$, " " " Z.
Let $Y = +b$, $X = 0$, " " " Z.
Let $Y = -b$, $X = 0$, " " " Z.

where $+a$ and $-a$ are the two radii which form the lateral diameter of the chest, *A*, and $+b$ and $-b$ are the radii of the anteroposterior diameter, *B*, of the chest. The lateral and anteroposterior diameters of the subject's chest were measured with obstetric calipers, and the

chest was treated as an elliptic cylinder. The calculations indicate the units of distance which the four points, one at each end of the two diameters, lie above or below the equator of the cylinder as defined by a horizontal plane through the center of the electrical field. It was found empirically that this equator generally lies 2 to 4 cm. below the fourth intercostal space, somewhat below the region where V_1 and V_2 precordial leads are taken. The positions of the four points for each subject were plotted on a graph folded into a cylinder having the same diameters as the subject's chest and a line was drawn connecting these points to resemble the pathway where a plane defined by these points would intersect the cylinder.

At the time the four bipolar leads were taken for calculating the spatial vectors, chest leads were also recorded using the Wilson central terminal with 5,000-ohm resistors and a 0.5-cm. exploring electrode. Leads were taken from the anterior and posterior surface of the chest at 1-inch intervals from above the level of the manubrium to below the umbilicus on the sternal and vertebral lines and, bilaterally, on the midclavicular, anterior axillary, midaxillary, and midscapular lines. Care was taken that the electrode paste did not connect adjacent electrode positions. The deflections were mounted on paper the same size as had been used to plot the null contour. The transitional QRS and T complexes (the deflections with as much positive as negative area regardless of their total amplitude) were identified on each line and these deflections connected by a smooth curve. This indicated the pathway of transitional QRS and T complexes around the chest.

In a second part of the present study it was desirable to simplify this method of calculating the spatial vectors in order to study the mean spatial vectors as a part of routine clinical electrocardiographic interpretation. By this modified method, the direction but not the magnitude of the mean QRS and T vectors in the frontal plane can be accurately determined from simple inspection of the three limb leads: if on one of the three limb leads the deflection is conspicuously smallest, the vector must be directed relatively perpendicular to the axis of that lead. If on the other hand, the deflection is conspicuously largest on one of these leads, the vector must be directed parallel to the axis of that lead. This can be readily seen by

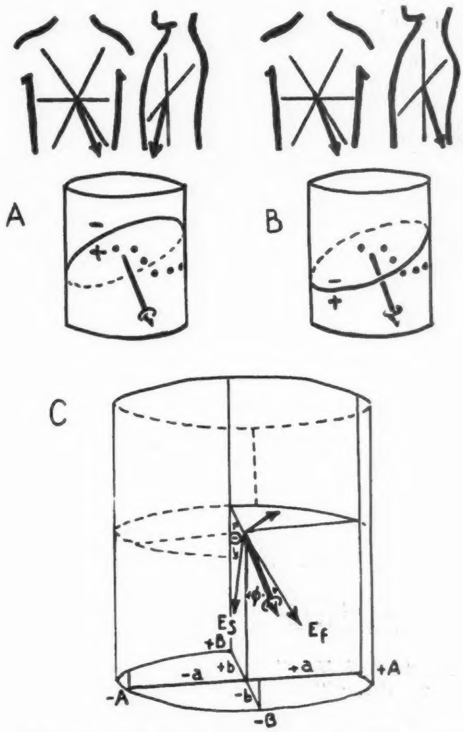

FIG. 2.—*A*, The vector has a slight anterior projection as seen in the sagittal plane calculations; accordingly, the null contour on the anterior aspect of the cylinder will lie superiorly to the equator of the cylinder. *B*, The vector is directed somewhat posteriorly, and therefore the null contour lies inferiorly to the equator of the cylinder. *C*, The projections of a mean spatial vector on three planes of the cylinder; E_s is the component on the sagittal plane and θ its angle with the anteroposterior axis of the cylinder; E_f is the component on the frontal plane, and ϕ its angle with the +90 degree axis in the frontal plane.

plotting test vectors on the triaxial system, with due regard to the polarities of this reference figure. With a little practice, the direction of the mean QRS and T vectors in the frontal plane can be calculated within a 10-degree error by simple inspection of the tracing. By compar-

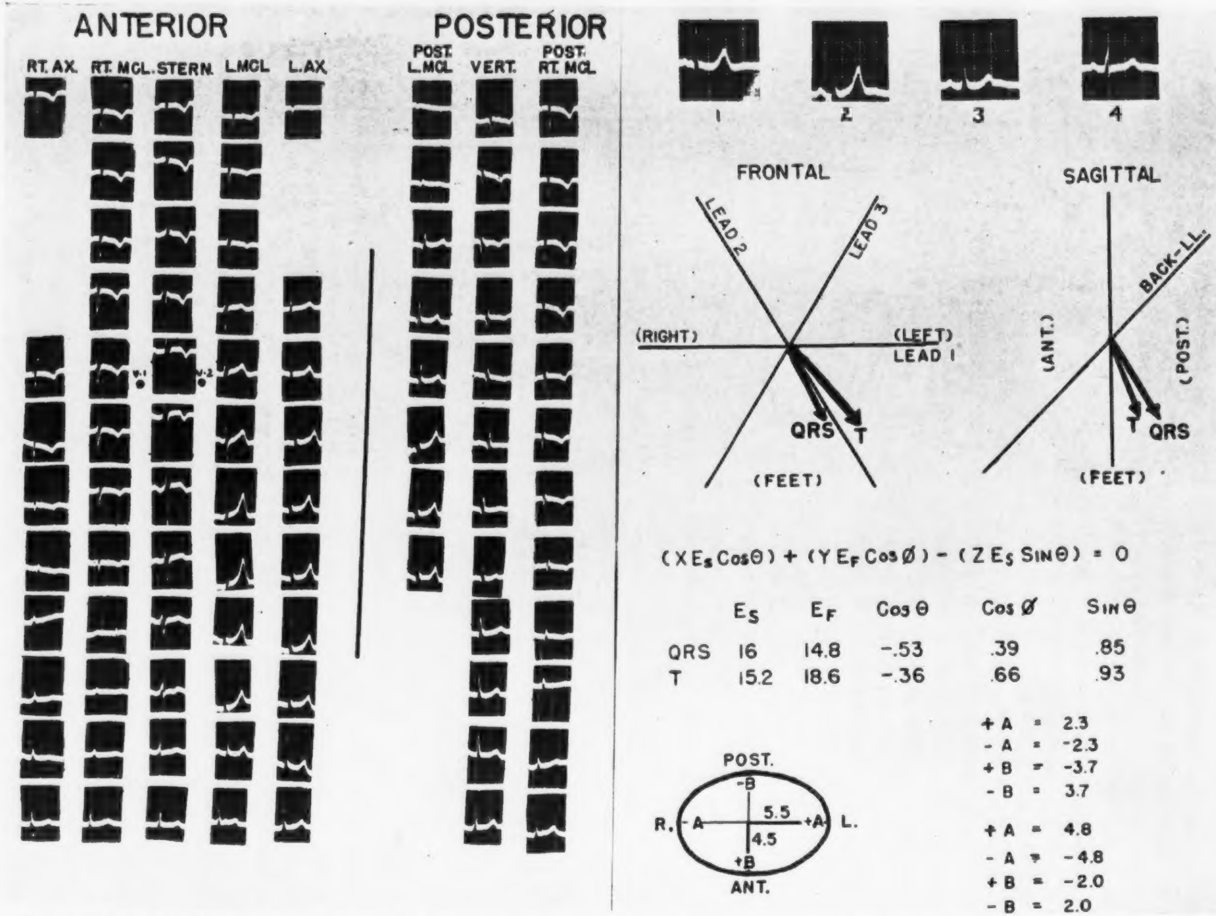

FIG. 3.—*A* (Left): V leads taken from the anterior and posterior chest of a normal young male subject (W. J., age 23, no cardiovascular disease); eight lines of tracings are presented. The absence of tracings from the upper ends of the axillary series is due to the attachment of the arms at these points. *B* (Right): The four spatial leads with the spatial QRS and T calculations. The projection on the frontal and sagittal planes, the chest dimensions, and the null contour calculations are presented.

ing the sizes of the QRS and T deflections of the limb leads and the back-to-left-leg lead, and by plotting these magnitudes on the biaxial system described earlier, the projection of the two vectors on the sagittal plane is determined.

The pathways of the null contours for QRS and T were compared with the pathways of transitional QRS and T complexes in three groups of subjects: (1) In 8 subjects the mathematically calculated null contours were compared with transitional pathways determined by the extensive anterior and posterior exploration described above. Two of these are illustrated; one of the subjects (figs. 3, 4, and 5) was a normal young man, the other (figs. 6 and 7) a 50 year old woman with a recent high lateral myocardial infarction. (2) In 20 subjects the visually calculated null contour was compared with extensive explorations of the anterior portion of the chest alone, in the manner outlined. (3) In over 1,000 consecutive subjects the visually calculated null contour (the back-to-left leg lead has been taken routinely in the Grady Memorial Hospital for the past year) was compared with the position of the transitional QRS and T deflections as they were encountered in routine V_1 to V_6 precordial leads.

A discussion of the validity of treating deflections from all surfaces of the body as due to the same electrical forces is appropriate before the results of this study are presented.

It has been shown by other workers that in a volume conductor the amplitude of a deflection varies inversely with the square of the distance from the dipole at the center of the conductor to the recording electrode.[1] This means that beyond a certain distance from the center of the field further displacement of the electrodes will result in negligible further change in amplitude of the deflection. In the human subject, this distance has been found to be 10 to 12 cm. from the heart.[6, 7] Electrodes more remote from the heart than this are, in effect, electrically equidistant from the heart, no matter what their differences in anatomic remoteness. Reversely, at such an electrode position all parts of the heart are electrically equidistant from the electrode.

In the present studies, however, electrode positions considerably less than 10 cm. from the heart are treated as electrically equidistant from all parts of the heart. The reason for this was that these experiments were concerned with the resultant electrical sign of the deflection and not the amplitude of the deflection. Adequate electrode remoteness will occur at points less distant from the heart in studies concerned with the distribution of electrical positivity and negativity than in studies concerned with the amplitude of the deflections. This can be explained in terms of current electrocardiographic theory by considering the properties of direct- and semidirect-lead QRS deflections.

A direct lead is taken by placing the recording electrode directly on the myocardium; in a semidirect lead the electrode is separated from the heart by electrically inactive but conducting tissue. In direct leads the QRS complex has been shown to consist of two parts: (1) an "intrinsic deflection," which is the descending limb of the R wave and is written when the portion of the myocardial surface immediately beneath the electrode undergoes activation, and (2) the "extrinsic components," which are the portions of the complex preceding and following the intrinsic deflection and represent the activation of the remaining surfaces of the ventricular muscle.[3]

Thus, in a direct lead the characteristics of the extrinsic components come nearer to reflecting the characteristics of the electrical field of the heart as a whole than does the amplitude of the deflection, for the amplitude is written by the intrinsic deflection, representing the very small subjacent portion of the myocardium. Because the amplitude-distance relationship for the various regions of the heart is an exponential one, nearly all but the subjacent portion of the heart are brought into electrical equidistance at electrode distances considerably less than 12 cm. from the heart. This can be seen in the tracings published in connection with amplitude-distance studies of the deflection as a whole, for the general contours of the deflections have become constant at electrode positions much less than 12 cm. from the heart.[6, 7] The contour of a deflection and its resultant electrical sign are principally functions of the

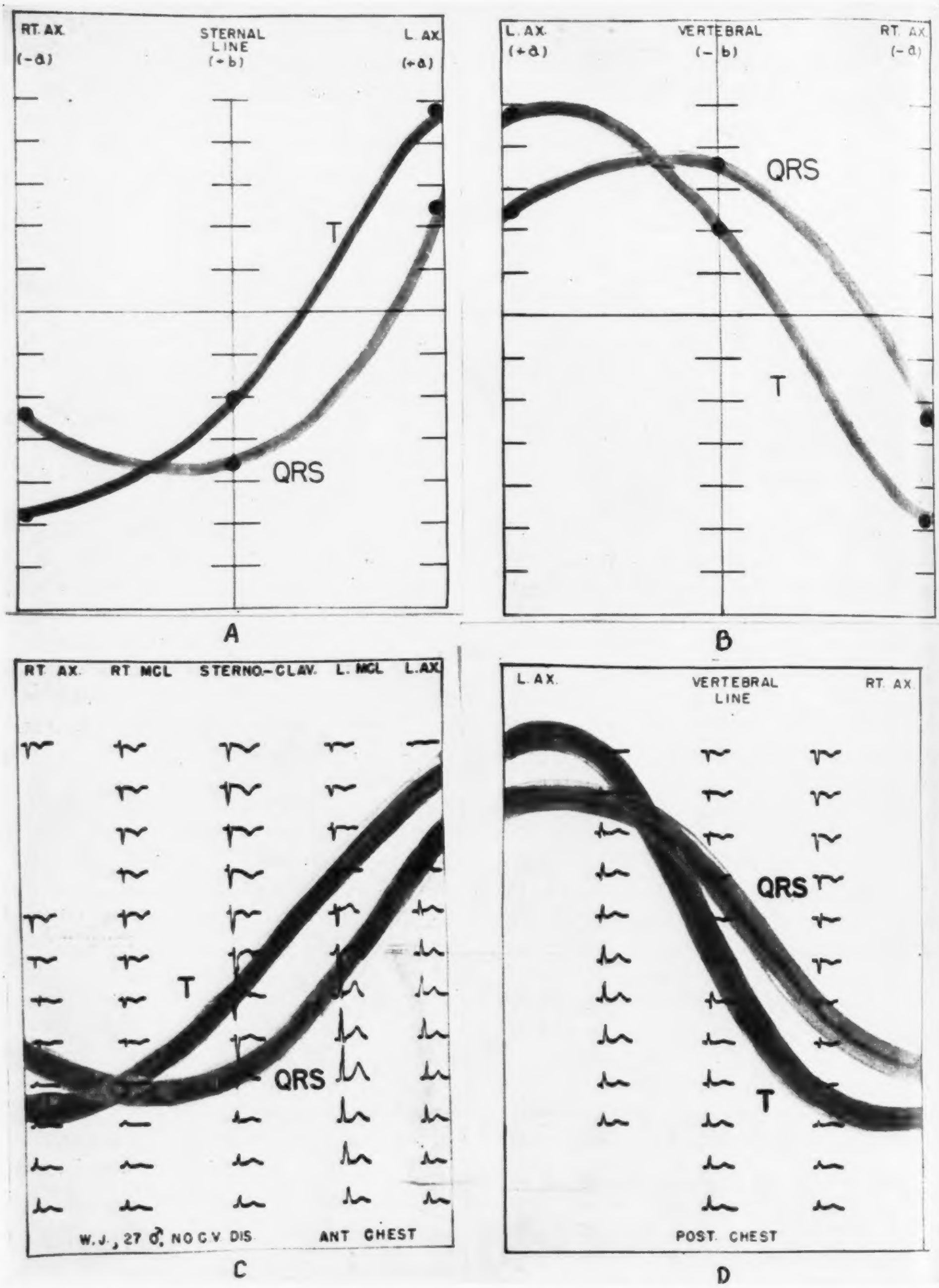

FIG. 4.—The tracings are from the same subject as those of figure 3. *A* and *B*: The null points on the anterior and posterior aspects of the cylinder are plotted and connected by a line which describes the pathway of intersection on the surface of the cylinder of a plane defined by these four null points for the QRS and T mean spatial vectors; these are lines of zero isopotentiality for the electrical field of each vector. *C* and *D*: QRS and T complexes from the V leads are copied onto paper the same size as was used for the null contour plotting; the transitional complexes are connected by a smooth curve which indicates the QRS and T transitional pathways for that subject.

extrinsic components of the deflection. Therefore, at electrode positions less than 12 cm. from the heart, under most circumstances, the resultant electrical sign of a deflection (whether it is a principally positive or negative deflection) reflects the mean electrical activity of the heart as a whole.

The resultant electrical sign of a deflection is a gross property of the deflection. To use such a property for the study of the electrical field of the heart might seem to be lacking in precision. Actually, however, the distribution of transitional complexes, those with a resultant electrical sign which is zero or null, is a quite precise property of a mean spatial vector, for the electrode writing such a deflection lies on a plane perpendicular to the vector. From this distribution of transitional complexes it is possible to determine the direction in space of the mean QRS and T electrical forces of the heart with reasonable accuracy, as these experiments demonstrate. The calculation gives no information as to the magnitudes of QRS and T forces. To determine their magnitudes from electrode positions less than 12 cm. from the heart would require more information about the electrical field of the heart than is at present available.

It must be recognized that body surface leads give at best only crude and general notions of the electrical processes of the heart. These limitations are often overlooked when theories or instruments of considerable intrinsic precision are adapted to the human electrocardiogram. However, the reverse has often been true, and sound principles governing the propagation of electrical forces have been delayed in their acceptance by an awareness of these limitations—even to the extent that some investigators have regarded the properties of the electrical field of the heart in the human subject as unique and not subject to recognized principles of physics.

There may also appear to be an oversimplification in comparing precordial deflections in the human subject to potential variations taking place on the surface of an idealized cylindrical volume conductor. After all, the

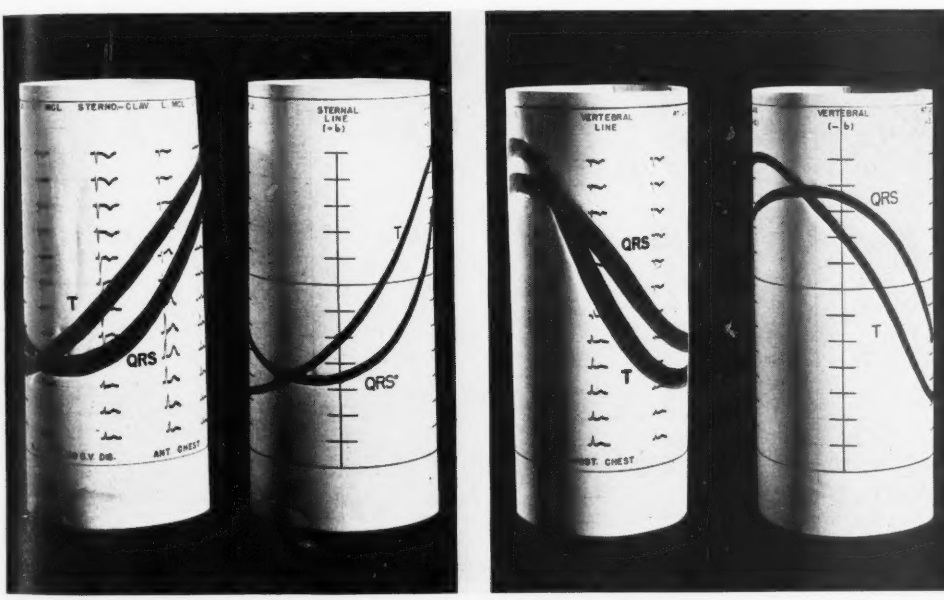

FIG. 5.—The recordings are from the same subject as those of figures 3 and 4. Comparison of null contours and transitional complex pathways on the anterior chest, *A*, and the posterior chest, *B*.

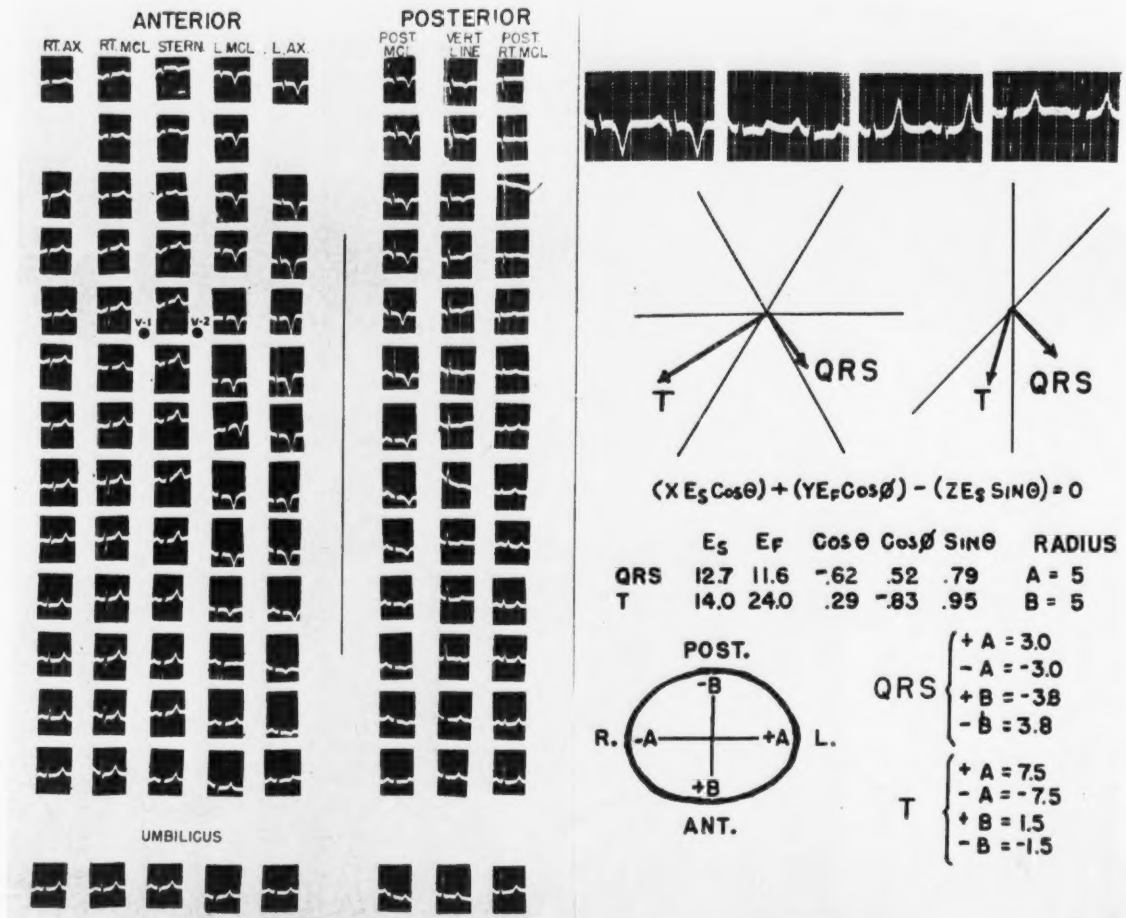

FIG. 6.—*A* (Left): Precordial leads taken from eight longitudinal lines on the anterior and posterior chest of a 53 year old woman (C. B.) with a recent high lateral myocardial infarction (note Q wave, elevated RS-T segment, and inverted T wave in the leads taken in the region of the left axilla). *B* (Right): The calculation of the null contour from the four spatial leads.

human chest is only crudely cylindrical, it is variable in its contour, the heart is anatomically eccentrically placed in the chest, and the intervening tissues are remarkably different in gross structure. Nevertheless, as others have indicated, the distribution of an electrical field in space is expressed by laws which are different from those governing anatomic distance and structure.[3] In an electrical sense, the chest proves to be remarkably similar to a cylinder with the heart at its center, as these studies demonstrate.

resembled projections from single central QRS and T spatial vectors. The forces from the ventricular surface nearest the electrode did not significantly dominate the deflections in this regard. Because this study has been concerned with the resultant sign of the entire complex, no conclusions can be drawn regarding the extent to which individual portions of the QRS complex in precordial leads were written as if by single central instantaneous vectors.

In Group 3 subjects, there was often a discrepancy of one or two, rarely three, V-lead

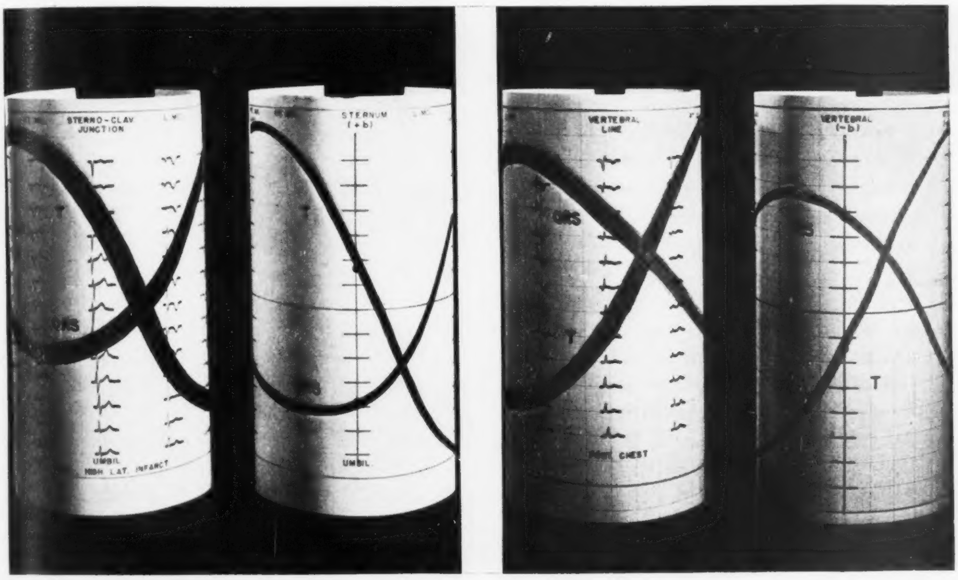

Fig. 7.—The recordings are from the same subject as those of figure 6. Comparison of the pathway of the QRS and T null contours with the pathways of transitional QRS and T complexes on the anterior chest, *A* (left), and the posterior chest, *B* (right).

Results

In all instances the distribution on the chest of transitional QRS and transitional T complexes closely followed the lines of zero isopotentiality, or null contours, calculated for the same subject's chest from his mean spatial QRS and T vectors. Figures 5 and 7 illustrate the similarity between the transitional pathways and the null contour in 2 cases taken from Group 1. In the thousand-odd cases studied, then, unipolar leads from the chest recorded deflections which in resultant direction

positions between the electrode position where the transitional complex was recorded and the electrode position through which the null contour was calculated to pass. In some instances this discrepancy was found to be due to inaccurately placed back or precordial electrodes. In other subjects, the simplifications and schematizations of the electrical field necessary for this type of study may have been the source of error. For example, the null contours were calculated for this group of subjects as if they all had chests of the same size, because chest

measurements were not available for this group of subjects. This must have introduced error in the calculations because, with other things equal, the size of the chest, especially its width, plays an important part in determining which precordial lead will write the transitional complex.

Also, in calculating the null contours, the zero point or origin of the spatial vector was considered to lie at the center of the chest. For most electrode positions on the chest this may have been valid, considering the electrical remoteness of these electrodes. In many instances, however, the precordial group of chest leads was undoubtedly sufficiently near the heart to record the resultant potentials as projections from a center point significantly to the left of the mid-line. If corrections had been made for these anatomic shortcomings, the results might have been improved, but this would have made the method more cumbersome and would not have increased its usefulness.

In certain of these subjects it is possible that the position of the null contour on the chest did not perfectly coincide with the position of the V lead with the transitional complex because there was significant domination of the V-lead deflections by the underlying myocardial surface—not enough to reverse the direction of the V-lead complexes, but enough to weight them for or against the occurrence of the transitional complex at the predicted precordial lead position. At areas of the chest where the myocardium is particularly close to the chest wall, for example V_4 position, this may have been true. Precise calculation of the degree of resultant positivity or negativity of the deflections at each electrode position might have disclosed more discrepancies. However, such calculations were not considered justified in view of the variables and sources of error they would involve.

Two subjects were encountered in this series of over 1000 cases in whom the underlying ventricular surface appeared to dominate the resultant direction of the deflection at a small area of the chest immediately overlying the apex of the heart. In both cases, positive T waves were predicted for the precordial leads V_1 to V_6 from the mean spatial T vector. However, the precordial tracings proved to have erect T waves at all positions except V_4 where a small isolated area of T negativity was found. The QRS complexes fitted well with the null contour established by the spatial QRS vector in these cases. Both subjects were young men with normal body builds and no clinical evidence of heart disease, and therefore this type of isolated T-wave inversion in the precordial leads must be considered to be normal. Further studies of the mechanism of this unusual type of T-wave disturbance will be reported elsewhere.

Discussion

This demonstration that the resultant electrical signs of the chest lead deflections reflect the direction in space of the mean QRS and T vectors sheds light on several theoretic aspects of human electrocardiography. For example, these findings affirm the hypothesis that the body is a relatively homogeneous volume conductor. In the experiments, unipolar leads were taken from many different sites on all surfaces of the chest. Since the characteristics of these deflections so closely agreed with the characteristics of the electrical field projected from spatial vectors, the body cannot have significantly distorted the distribution of the electrical forces. This uniformity of conductivity, first suggested by Einthoven, has been challenged by many workers in the past, but has received more and more support in recent years. It is a fundamental assumption in most current methods for electrocardiographic interpretation, and there is now little room to doubt that it is satisfactorily valid for clinical electrocardiographic methods. For the same reason, the experiments lend support to the assumptions upon which spatial or three-dimensional electrocardiography is based.[4, 5]

The validity and usefulness of the Wilson central terminal is demonstrated by these studies. Under the circumstances of these experiments, the central terminal was found to establish a reference point which was satisfactorily near the zero point in the sagittal as well as the frontal plane of the body. Ashman[11] studied the relationship of the central terminal

to the precordial leads by a different method and also concluded that it establishes a reference point reasonably near the center of the electrical field in three-dimensional space.

The present study assumes the heart's electrical field to have a spatial distribution in the body such that the four spatial electrodes can be considered to form an isosceles tetrahedron electrically. In this figure, the zero point of the field lies at the mid-point of the frontal plane and equidistant electrically from the four electrodes. The error is evidently not great when the precordial lead deflections are treated as reflecting the mean direction of QRS and T forces arising from this point.

These studies also demonstrate that conventional precordial leads can be used to measure certain spatial characteristics of the QRS and T forces of the heart. Einthoven introduced his three limb leads thirty years ago as a method for studying the characteristics of these forces as they are projected on the frontal plane of the body. However, the clinical correlation of abnormalities in these leads with various types of cardiac disorders rapidly outstripped the growth of knowledge of the mechanisms producing these electrical abnormalities. Accordingly, the three leads have not been widely used to measure the electrical forces involved; instead, clinical electrocardiography has come to be based upon recognizing wave forms in the complexes of these and other often randomly selected leads for the interpretation. Ultimately, of course, clinical electrocardiography must be based upon an analysis of the changes in the electrical forces of the heart if it is to become a rational and objective clinical procedure. Principally owing to the work of Wilson and his colleagues, this method of interpretation is coming nearer to realization, and the present article is a step in this direction.

The usefulness of studying the electrocardiogram in terms of the spatial vectors is illustrated by the following example. The QRS complex in a particular precordial lead, V_1 for example, may resemble the QRS complex of one of the unipolar limb leads, V_R for example. This has been adduced to mean that, in this instance, the right side of the electrical field faces the right arm. This interpretation has been found useful in defining the position and rotation of the heart[8]; however, it has never been clear why the leads with similar QRS complexes often have dissimilar T waves. Thus, the QRS may be inverted in both V_1 and V_R but the T wave may be upright in V_1 and inverted in V_R in the same subject. The explanation for this nonconcordance between QRS and T complexes in the two leads becomes apparent when the positions of the V_1 and V_R electrodes on the chest are considered in the light of the direction of the mean spatial vectors. Since the mean QRS and T vectors do not necessarily have the same direction in a given subject, the distribution of positive and negative fields for each on the surface of the chest will be different. Thus, in a normal subject the QRS vector is often directed to the left and somewhat posteriorly. Therefore, the null contour, defining where transitional QRS complexes will be recorded, runs longitudinally down the left side of the chest. The area of the chest to the right of this line is electrically negative, and electrodes placed here will therefore write deflections which are inverted in their resultant direction. The area to the left is positive and deflections on this surface will be resultantly upright in direction. Since the electrodes for V_1 and V_R are placed to the right of this line, both leads will write downward deflections, and these QRS deflections will "resemble" one another to this extent. The spatial T vector on the other hand may be directed vertically and slightly anteriorly. The pathway of transitional T waves will, in such a case, lie transversely across the upper chest. V_1 and V_R electrode positions lie on opposite sides of this transitional zone, and the T wave of V_1 will therefore be erect, while the T wave of V_R will be negative or inverted.

Using vector principles, much of empirical electrocardiography can be reduced to vector generalizations which greatly simplify clinical interpretation. For example, to make the electrocardiographic diagnosis of ventricular hypertrophy, it need only be remembered that the spatial QRS vector tends to be directed toward the ventricle with the larger relative muscle mass. Accordingly, in right ventricular hyper-

trophy the mean spatial QRS vector should drift to the right and anteriorly. Under these circumstances the limb leads will record right axis deviation. In the precordial leads, the pathway where transitional QRS complexes will be recorded for a vector with this direction runs obliquely across the upper left side of the chest. The pathway will cross the precordium near the V_4 precordial electrode position. V leads taken to the right of this pathway will write QRS deflections which are upright in resultant direction because their electrode positions lie in the area of electrical positivity for this spatial vector direction. The QRS complexes in V leads taken to the left of this line will be inverted in resultant direction because this is the area of electrical negativity. This is the same distribution of QRS complexes that has been associated with right ventricular hypertrophy in all empiric studies of the electrocardiogram in this disorder.

The many variations from this pattern of distribution of upright and inverted precordial QRS complexes can be easily evaluated by determining the direction of the mean spatial QRS vector in the given case. The T vector, normally relatively parallel with the QRS vector in space, tends to become directed away from regions of ischemia and of hypertrophy. Accordingly, by studying the distribution of positive and negative T waves in the various leads, the direction of the spatial T vector can be determined, and from this the location of the area of disturbed electrical activity can in general be identified.

The ventricular gradient is a concept which Wilson and co-workers introduced to define a fundamental relationship between the QRS and T vectors in the frontal plane of the body. This concept is the basis for a more rational and accurate method for interpreting the limb lead electrocardiogram.[12, 13] The results of the experiments reported here indicate that the precordial leads can also be interpreted in terms of the ventricular gradient. The mean directions of the spatial QRS and T vectors can be readily determined from the three limb leads and the six precordial leads. It is thus possible to determine the angle between the two vectors (the QRS-T angle) in space, and this angle is an expression of the ventricular gradient.

The accurate calculation of the magnitude and direction of the ventricular gradient is too time-consuming and exacting for routine clinical use.[13, 14] With a little practice, however, the spatial QRS-T angle can be determined from simple inspection of the conventional limb and precordial leads. This is done by first determining the direction of the QRS and T vectors in the frontal plane, using the triaxial reference system with due regard to its polarity. The limb lead on which the QRS is conspicuously largest or smallest as a resultant deflection is identified. The QRS vector will have a direction parallel with the axis of the lead with the largest deflection, or perpendicular to the axis of the lead with the smallest deflection. The same procedure is followed for the T vector, and with experience the directions of the two vectors in the frontal plane can be determined by inspection within a 10-degree error.

In order to determine how far anteriorly or posteriorly from its frontal plane projection a spatial vector is directed, the precordial lead with the transitional deflection is identified. As has been shown in the above experiments, the electrode position where this complex occurs tends to lie on a plane which is perpendicular to the spatial vector at its origin. One can easily visualize, then, how far anteriorly or posteriorly from the frontal projection the spatial vector must be tilted to have its plane pass through this particular V-lead position. To visualize the vector in space, it is helpful to draw the frontal outline of the chest (or, simply a cylinder) with the frontal plane vector drawn at the center of the figure in the direction determined for it from the three limb leads (fig. 2). The position of the precordial V-lead which contained the transitional complex is marked on the figure. The spatial vector will, of course, perfectly superimpose on the frontal plane projection in this view. The line where the plane intersects the surface of the cylinder can then be drawn on the figure to pass through the point identifying the precordial electrode position with the transitional complex. Once the method is understood, the QRS-T angle in

space can usually be evaluated without using the diagram, the entire procedure taking no more time than conventional methods for reading tracings. The QRS-T angle rarely exceeds 45 degrees in the frontal plane[14] or 50 degrees in space[4] in the normal subject, and such criteria as these can form the basis for the clinical interpretation of the electrocardiogram.

This modification of existing methods for electrocardiographic analysis makes clinical interpretation of the electrocardiogram more rational and objective, for the vectorial method tends to be a quantitative study of the electrical forces of the heart instead of a description of the deflections on arbitrarily selected leads. Furthermore it greatly simplifies learning to read the electrocardiogram, for all possible variations and combinations in resultant direction of the QRS and T waves on all possible leads anywhere on the body are implicit in the directions of these two mean vectors. The memorizing of deflection sizes and combinations on the various unipolar and bipolar limb leads and precordial leads, and the taking of additional unusual leads become largely superfluous. The accuracy of the interpretation is enhanced because variations in the deflections due to altered position of the heart are quickly identified, and because the precision of the ventricular gradient concept is incorporated into the method. A more detailed description of the vector method and its usefulness for electrocardiographic interpretation will be presented elsewhere.

Conclusions

1. The relationship of the QRS and T deflections of the precordial leads to the mean spatial QRS and T vectors has been studied.

2. A method is presented for determining the distribution of QRS and T positivity and negativity on the surface of a cylindrical volume conductor the shape of the subject's chest from the mean spatial QRS and T vectors. In a large number of subjects this distribution closely resembles the distribution of resultant positive and negative QRS and T deflections on the chest as determined by conventional V-lead methods.

3. This similarity in distribution indicates that when precordial V leads are studied for their resultant electrical sign, that is, whether they are principally positive or negative deflections, they reflect the mean direction in space of the electrical forces of the heart as a whole; the portion of the myocardium directly beneath the electrode does not appear to dominate significantly the precordial deflection as far as its resultant direction is concerned under most circumstances.

4. Precordial leads can therefore be interpreted by the same vector technique already demonstrated to be of such value in interpreting limb leads. This method reduces interpretation to an analysis of the angle between the mean QRS and T vectors in space, which proves greatly to simplify the reading of precordial and limb leads, enhances their accuracy, and provides a more rational basis of electrocardiographic interpretation.

Acknowledgment

The author wishes to thank Professor James H. Purks, Department of Physics, Emory University, for his assistance in the mathematical aspects of this study.

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A Study of the Spatial Vectorcardiogram in Left Bundle Branch Block

By J. Frank Pantridge, M.D., J. A. Abildskov, M.D., G. E. Burch, M.D., and J. A. Cronvich, M.S.

A method of vectorcardiography, in which the projections of the spatial vectorcardiogram in various planes of an equilateral tetrahedron reference system are recorded, has been applied to the study of left bundle branch block. Results suggest that the method employed may provide information relative to the state of the myocardium and the extent of myocardial lesions which is not evident from electrocardiographic examination.

EXPERIMENTAL evidence has shown that the electrocardiographic pattern regarded as indicative of left bundle branch block may result from interruption of the left bundle branch by a local lesion.[1] Clinical and pathologic evidence, however, has been presented to suggest that more commonly this electrocardiographic pattern results from diffuse myocardial damage associated with hypertrophy and dilatation of the left ventricle.[2, 3]

The clinical state and the poor prognosis of the majority of patients in whom left bundle branch block is diagnosed indicate that this electrocardiographic abnormality is usually associated with grave myocardial damage. However, a small proportion of patients with this disturbance in conduction show minimal clinical evidence of myocardial disease; it is presumed that in these the bundle branch has been interrupted by a local lesion.

The impossibility of determining by ordinary electrocardiographic methods the extent of a lesion responsible for or associated with left branch block prompted this study of the spatial vectorcardiogram in that condition. It was hoped that by analysis of the spatial vector it might be possible to determine whether the block arose from a generalized abnormality of the conducting tissue or cardiac muscle of the left ventricle, from involvement of the septum by an anterior or posterior myocardial infarct, or from interruption of the bundle branch by a well localized lesion.

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Materials and Method

Twenty-eight patients from the wards of the Charity Hospital, whose electrocardiograms had been interpreted as indicative of left bundle branch block, were selected for study. The QRS interval in all cases measured 0.12 second or more, and in 23 cases unipolar leads from the left side of the precordium showed definite delay in the onset of the intrinsicoid deflection. The electrocardiograms of 4 subjects (Subjects 3, 4, 7, and 11) showed QRS intervals of 0.13 to 0.16 second but did not show broad, flat-topped or splintered R waves in the precordial leads. Such tracings represent a special problem of interpretation and are not universally considered to indicate left bundle branch block.

The spatial vectorcardiograms were recorded by the method described by Wilson and Johnston[4, 5] as modified in this laboratory. This method employs as a reference system the equilateral tetrahedron of Wilson.[6] The standard limb electrodes and a back electrode placed approximately 3 cm. to the left of the seventh dorsal vertebral spine were used. The projections of the movement of the spatial vector on the frontal and sagittal planes of the tetrahedron were recorded simultaneously by means of two cathode-ray tubes.

The connections of the cathode-ray tube used to record the frontal vectorcardiogram are similar to those described by Wilson and Johnston.[4] The right and left arm electrodes were connected to the plates of the cathode-ray tube producing horizontal deflections; the plates producing vertical deflections were connected to the Wilson central terminal and to the left foot. The connections were so arranged that relative positivity of the left arm produced a

TABLE 1.—*Clinical Data*

Subject No.	Age (Yrs.)	Sex	Cardiac Enlargement*	B.P.†	Congestive Failure‡	History of Angina	History Suggesting Coronary Occlusion	Clinical Diagnosis
				Group I				
1	62	M	++	230/75; 148/60	+	−	−	H.C.V.D.,§ syphilitic aortic regurgitation
2	60	M	+	108/80	+	−	−	A.S.H.D.‖
3	48	M	++	170/90	+	−	−	H.C.V.D.
4	72	M	+++	230/110; 188/74	L.V.	−	?	H.C.V.D.
5	81	M	+++	180/90	−	−	−	H.C.V.D. and A.S.H.D.
6	57	M	+++	102/86	+	−	−	A.S.H.D.
7	76	M	+	150/100	−	−	−	Bronchial carcinoma and H.C.V.D.
8	30	F	++	140/40	+	−	−	Syphilitic aortic regurgitation
				Group II				
9	74	F	+++	185/95	++	−	−	H.C.V.D.
10	78	M	+++	200/120; 130/90	++	?	−	H.C.V.D.
11	64	M	+++	190/135; 140/98	+	−	−	H.C.V.D.
12	51	F	+++	234/158	+	+	?	H.C.V.D.
13	44	F	sl.	250/120	L.V.	?	−	H.C.V.D.
14	64	F	++	160/110	+	−	−	H.C.V.D.
				Group III				
15	74	M	−	120/75	−	−	−	A.S.H.D.
16	48	F	++	190/135	+	−	+	H.C.V.D. and A.S.H.D.
17	64	F	+	134/78	+	+	−	A.S.H.D.
18	60	F	++	105/70	+	+	+	A.S.H.D.
19	77	M	++	220/110	++	−	−	H.C.V.D.
20	67	M	+	100/84	+	−	−	A.S.H.D.
21	68	F	+	185/100	+	−	+	H.C.V.D. and A.S.H.D.
22	55	F	++	115/75	++	−	−	A.S.H.D.
23	49	F	sl.	230/130	L.V.	+	−	H.C.V.D.
24	47	F	++	164/110; 124/64	+	−	−	H.C.V.D. and A.S.H.D.
25	59	M	+++	140/90	+++	−	−	A.S.H.D.
				Group IV				
26	74	M	sl.	170/90	−	−	−	Duodenal ulcer
27	65	M	−	155/70	−	+	−	Benign prostatic enlargement and H.C.V.D.
28	58	M	sl.	158/96	−	−	−	Bronchiectasis

* Degree of cardiac enlargement is graded as − = no enlargement, sl = slight, + = moderate, ++ = severe, +++ = extreme.

† When two values for blood pressure are given, the first is the highest value recorded in the past and the second the value obtained at the time the vectorcardiogram was recorded. When one value is given, it is that obtained at the time the vectorcardiogram was recorded.

‡ Severity of congestive failure is graded as − = none, + = moderate, ++ = severe, and +++ = extreme. Isolated left ventricular failure is indicated by L.V.

§ H.C.V.D. = hypertensive cardiovascular disease.

‖ A.S.H.D. = arteriosclerotic heart disease.

deflection of the beam to the left (or to the right, as viewed by the observer). The calibration is such that 1 millivolt introduced into the horizontal circuit produces a deflection of the electron beam of 1.0 inch on the oscillographic screen and 1 millivolt introduced into the vertical circuit produces a deflection of 1.7 inches. The cathode-ray tube used to record the sagittal vectorcardiogram was so connected that horizontal deflections were obtained from the Wilson central terminal and the back electrode, the calibration being 1.2 inches per millivolt. Relative positivity of the back electrode resulted in movement of the electron beam to the right (as viewed by the observer when facing the sagittal plane from the left). The vertical deflections in this tube were obtained from the Wilson central terminal and the left foot, the calibration being a deflection 1.7 inch per millivolt. Relative positivity of the foot electrode yielded a downward deflection of the beam.

The projection of the locus of the spatial vector onto the superior, right, and left planes of the tetrahedron was also obtained by selecting proper combinations of electrodes. The calibrations used are necessary "standardizing factors" because the potential differences are scalar quantities which are treated as vectors.[7]

Wire models representing the QRS s$\check{E}$-loops and T s$\check{E}$-loops were constructed from simultaneous photographic records of the frontal and sagittal vectorcardiograms, and the constructions were checked by records of the projection of the movement of the vector on the superior, right, and left surfaces of the tetrahedron.

Electrocardiograms showing the standard leads, unipolar limb leads, precordial Leads V_1 to V_6 and Lead V_B were obtained for the majority of subjects at the time of recording of the vectorcardiogram. Electrocardiograms (standard and precordial Leads V_1 to V_6) of the remainder of the subjects were obtained from the hospital files. The interval between recording of the electrocardiogram and of the vectorcardiogram of these subjects was usually a few days. Correlation of the electrocardiogram, spatial vectorcardiogram, and clinical features was therefore possible. The clinical features considered most relevant to this investigation are recorded in table 1. Cardiac size and position were confirmed by roentgenographic examination. When present, enlargement involved predominantly the left ventricle.

Results

Drawings constructed from tracings of the simultaneously recorded frontal and sagittal vectorcardiograms are illustrated in figures 1 through 4. For purposes of presentation the triaxial reference system was used in the frontal plane. Angles in the sagittal plane are measured similarly with the ± 180 degree axis located anteriorly. The term "axis of the loop" is used to indicate a straight line drawn from the origin of the loop to its most distant point. This bears no constant relationship to the mean electric axis.

With one exception (the frontal plane loop of Subject 26), the projections of the QRS s$\check{E}$-loop on both the frontal and sagittal planes are inscribed in a counterclockwise direction. As would be expected from the observed S-T segment shift, the QRS s$\check{E}$-loop failed to return to the isoelectric point, its termination and the initial portion of the T s$\check{E}$-loop being displaced away from the origin. For this reason a closed T s$\check{E}$-loop was not written. The point at which the QRS s$\check{E}$-loops and T s$\check{E}$-loops become continuous was readily recognized on the oscillographic screen by abrupt deceleration of the fluorescent beam. This point of junction is indicated in the illustrations by the letter *J*.

For purposes of description only the subjects have been divided into four groups on the basis of similarity of the recorded QRS s-$\check{E}$ loops:

Group I. The QRS s$\check{E}$-loops of Subjects 1 through 8 (figs. 1 and 7) tended to enclose a single plane area facing anteriorly and somewhat to the left. The projection on the frontal plane enclosed a wide area located mainly in the first and second sextants of the triaxial reference system and the projection on the sagittal plane a relatively narrow area. Both the axis of the sagittal projection of the QRS s$\check{E}$-loop and that of the frontal axis lay between -30 and -70 degrees. The QRS s$\check{E}$-loops in this group presented a relatively smooth, oval or rounded contour.

Group II. The QRS s$\check{E}$-loops of Subjects 9 through 14 (figs. 2 and 7, Subject 11) were elongated and directed upward, backward, and to the left. The areas enclosed by their projection on both the frontal and sagittal planes were small. The axis of the frontal projection lay between -30 and -70 degrees and that of the sagittal projection between -40 and -45 degrees.

The majority of the spatial QRS s$\check{E}$-loops in this group presented an irregular contour.

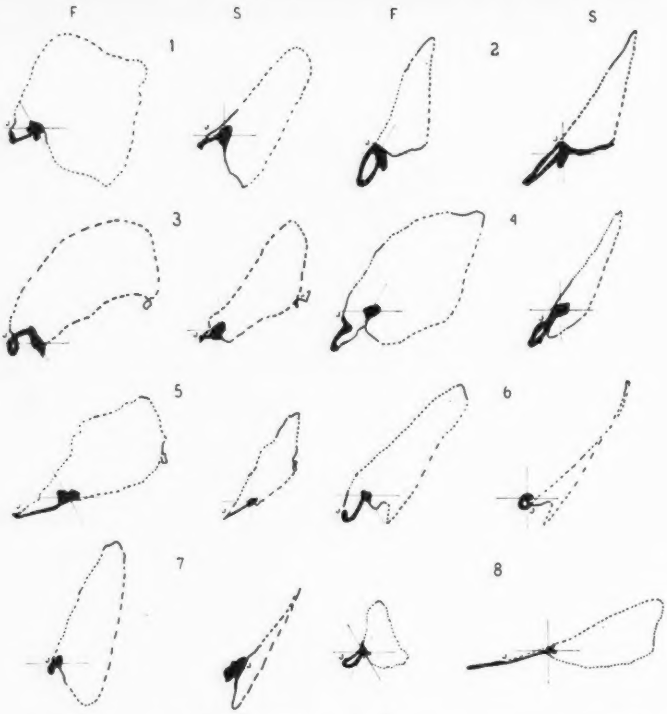

FIG. 1.—Group I: QRS sĚ-loops and T sĚ-loops of Subjects 1 through 8.

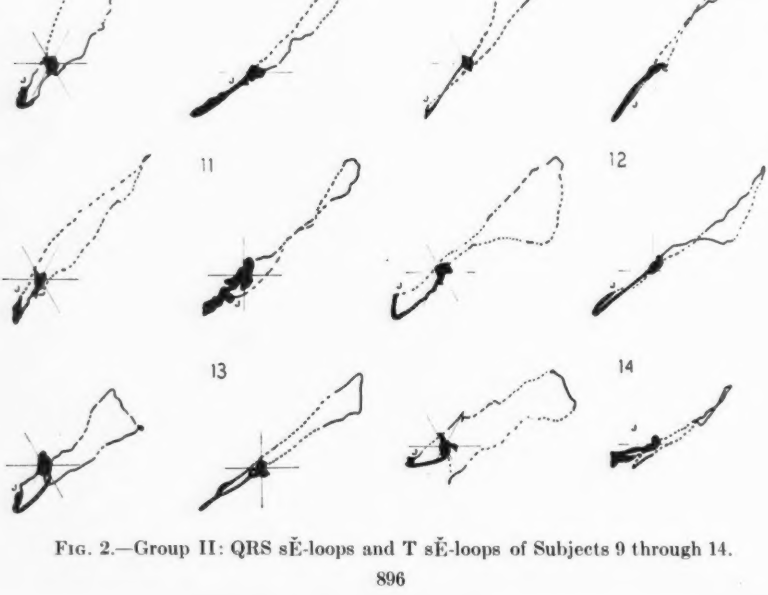

FIG. 2.—Group II: QRS sĚ-loops and T sĚ-loops of Subjects 9 through 14.

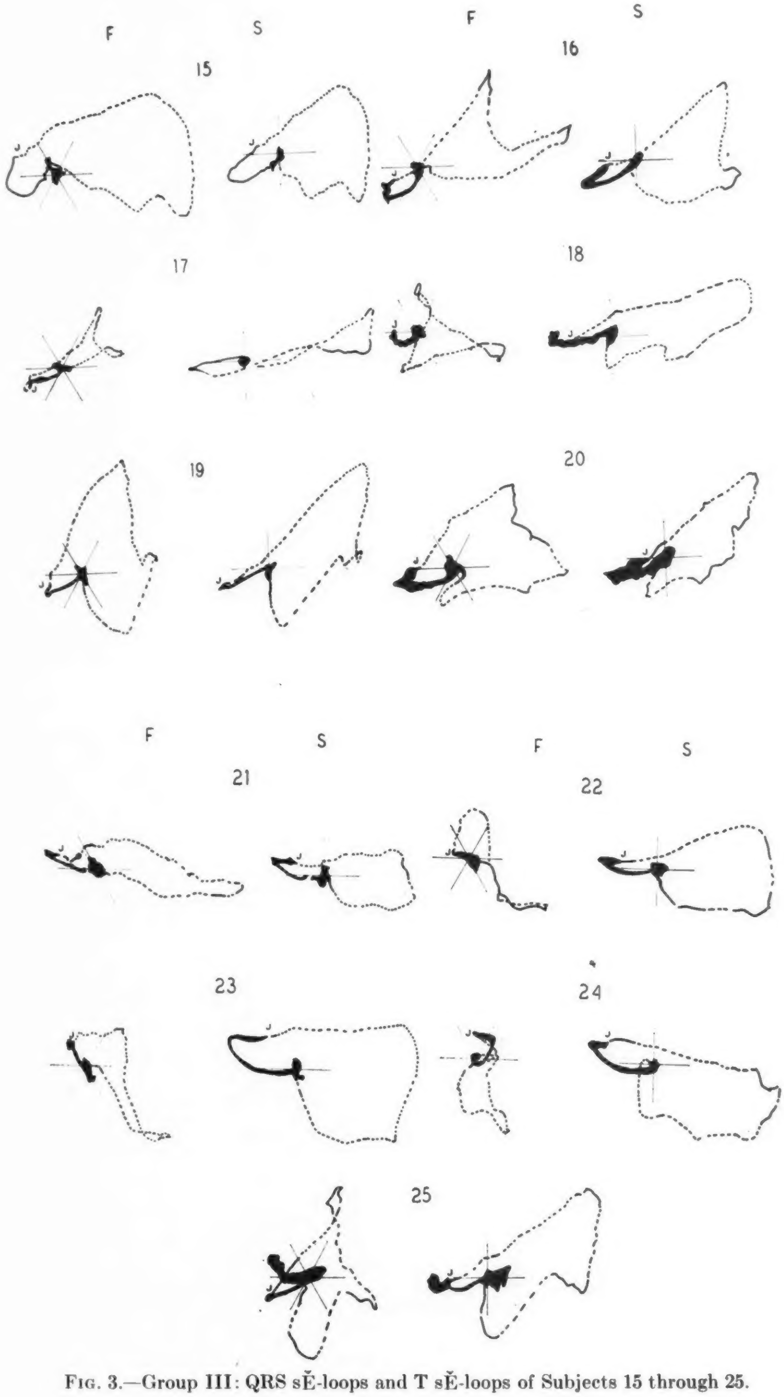

FIG. 3.—Group III: QRS sĚ-loops and T sĚ-loops of Subjects 15 through 25.

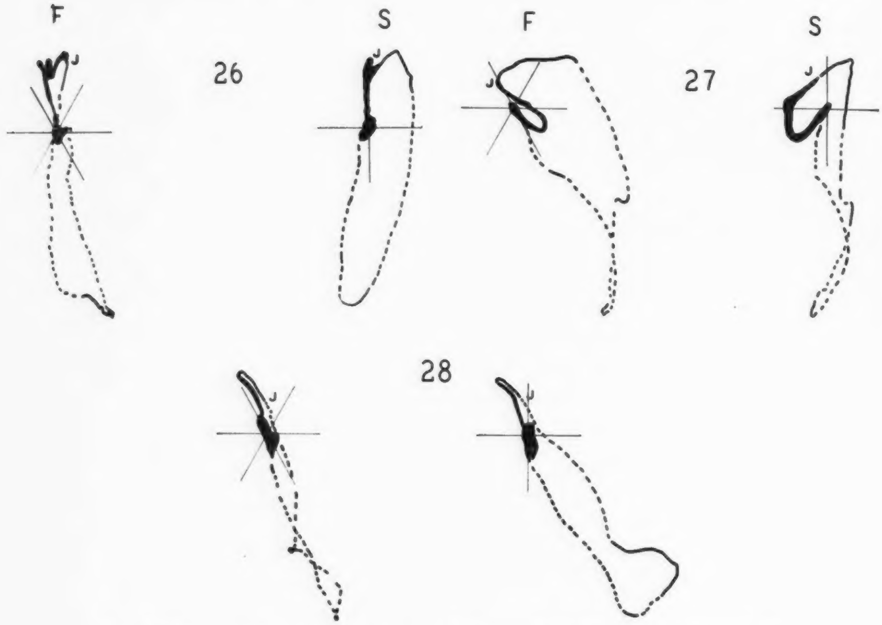

FIG. 4.—Group IV: QRS sĚ-loops and T sĚ-loops of Subjects 25 through 28.

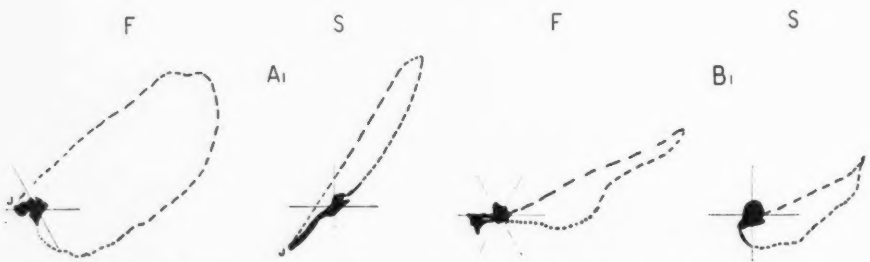

FIG. 5.—QRS sĚ- and T sĚ-loops of two patients with gross left ventricular hypertrophy.

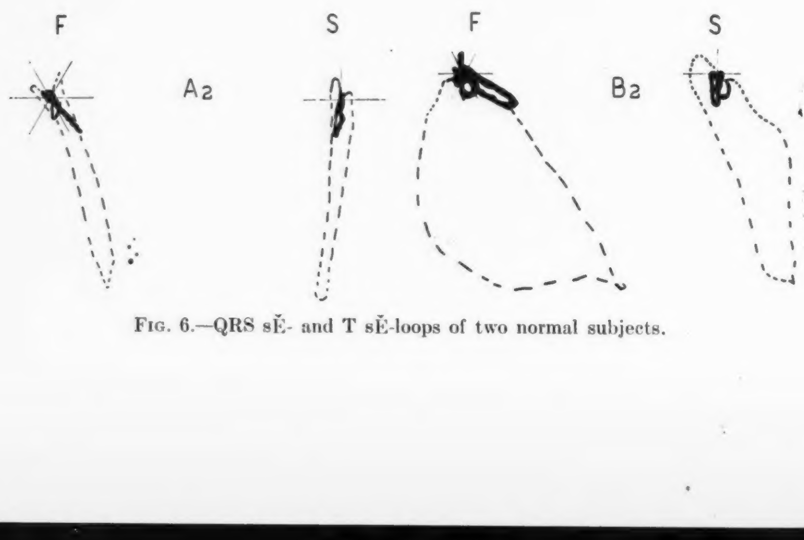

FIG. 6.—QRS sĚ- and T sĚ-loops of two normal subjects.

Those of Subjects 10, 11, 12, and 14 were rotated on their longitudinal axis and did not, therefore, enclose a single plane area.

Group III. The QRS sĚ-loops of Subjects 15 through 25 (figs. 3 and 7, Subject 18) were directed backward and to the left. The axis of the frontal projection lay between +70 and −70 degrees, that of the sagittal projection between +20 and −60 degrees. Many of the QRS sĚ-loops in this group showed extensive indentations or irregularities, especially on the long limbs, and it was largely on this basis that these were classified together. The QRS sĚ-loops of Subjects 22, 23, and 24 were projected almost directly backward and enclosed a wide, roughly rectangular plane area so rotated that the left surfaces were directed slightly upward. With the exception of these three subjects the projections of the QRS sĚ-loops on the frontal and sagittal planes enclosed approximately equal areas. The contour of the QRS sĚ-loops in this group were irregular or angular.

Group IV. The QRS sĚ-loops of Subjects 26, 27, and 28 (figs. 4 and 7, Subject 26) were elongated and differed greatly from those of the other groups in their downward direction. The axis of the frontal projection lay between +70 and +80 degrees, that of the sagittal projection between +60 and +100 degrees. Both projections encompassed relatively small areas. The QRS sĚ-loops of Subject 26 enclosed a plane area, presented a smooth contour, and resembled closely in character and direction that of the normal vectorcardiogram.

Discussion

The known variability of the extent and distribution of the pathologic changes associated with left branch block and the impossibility of pathologic correlation, except in 2 subjects, make it difficult to draw from this study more than tentative conclusions. The spatial vectorcardiographic pattern in the subjects of Group I and that in subjects with clinical and electrocardiographic evidence of left ventricular hypertrophy exhibited a striking resemblance (figs. 1, 5, and 7, Subjects 7 and A_1). Figure 5 shows the frontal and sagittal projections of the QRS sĚ and T sĚ-loops of 2 subjects with severe left ventricular hypertrophy. The similarity between these spatial loops and those of the subjects in Group I suggests that in some cases an electrocardiographic pattern interpreted as indicative of left branch block may in fact represent an expression of severe left ventricular hypertrophy. In this connection it may be noted that in Subject 7 of Group I, in whom death occurred from bronchial carcinoma, the only cardiac abnormality found at autopsy was hypertrophy and dilatation involving particularly the left ventricle, although detailed serial sections of the region of the left bundle branch were not obtained.

With one exception (Subject 13) the subjects in Group II showed severe to extreme cardiac enlargement and evidence of moderate to severe chronic congestive heart failure. The QRS sĚ-loops of these subjects enclosed a much narrower area and had a more irregular contour than those of the subjects in Group I. It would seem that these characteristics of the loops are most likely to arise from presence of diffuse myocardial damage.

Group III is of particular interest in that three of the subjects in this group had exhibited a clinical syndrome typical of coronary occlusion. The pattern of the QRS sĚ-loops of these subjects was similar to that which might be expected to result from failure of the anterior or anterolateral surface of the left ventricle to contribute to the formation of these spatial loops. The movement of the efferent portion of the QRS sĚ-loop in Subjects 18, 20, 24, and 25, resulting in the appearance of Q waves in Leads I or V_B of the conventional electrocardiogram, suggests the probability of infarction of the septum as well.

The clinical state of the subjects in Group IV differed greatly from that of the subjects in the other groups. In the subjects of Group IV, cardiac enlargement was slight or absent, and there was no evidence of congestive failure. The QRS sĚ-loops of these subjects, as indicated previously, tend to resemble those of normal subjects.

The QRS sĚ-loop of Subject 26 in this group differed from the normal only in its rate of inscription and failure to return to the isoelectric point (fig. 4). This patient died following

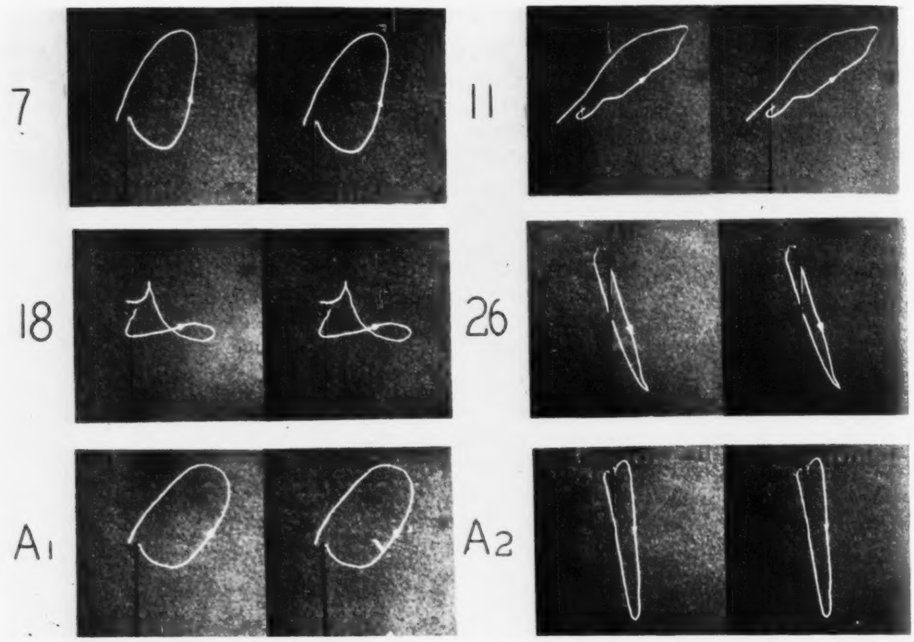

FIG. 7.—Stereoscopic photographs of wire models representing QRS sĚ-loops and T sĚ-loops. (See text.)

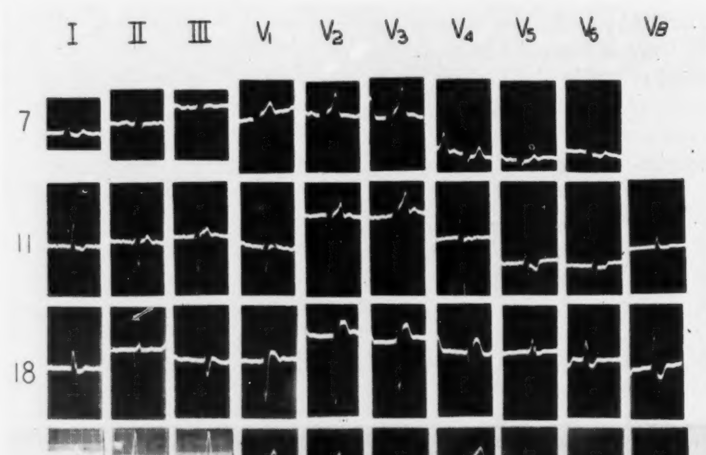

FIG. 8.—Electrocardiograms of subjects whose QRS sĚ-loops and T sĚ-loops are shown in figure 7.

the occurrence of a massive hemorrhage from a duodenal ulcer, and postmortem examination revealed diffuse, patchy interstitial fibrosis, particularly of the septum. Only slight coronary sclerosis and slight left ventricular hypertrophy were present. It seems probable that in this patient bundle branch block arose from a local lesion.

For purposes of comparison the frontal and sagittal projections of the QRS sĚ-loops and T sĚ-loops of two normal subjects are presented in figure 6 and in figure 7, Subject A_2. In both of these subjects the projection on the frontal plane of the QRS sĚ-loop moved in a clockwise direction and the projection on the sagittal plane counterclockwise.

Photographs of the wire models of the QRS sĚ- and T sĚ-loops of a representative subject from each group are shown in figure 7. These may be viewed stereoscopically by placing a card between a pair and moving the page slowly toward or away from the eyes until a three-dimensional effect is obtained. The QRS sĚ- and T sĚ-loop models of a subject with left ventricular hypertrophy and those of one of the normal subjects are also shown. The electrocardiograms of these selected subjects, with the exception of the normal, are shown in figure 8.

Summary

The spatial vectorcardiographic pattern in twenty-eight subjects with electrocardiographic evidence of left bundle branch block is described. The wide variation in this pattern was noted, and the subjects were divided into four groups on the basis of similarity of the QRS sĚ-loops.

The spatial vectorcardiographic pattern of one group (Group I) resembled that of some subjects with severe left ventricular hypertrophy. Postmortem examination of one patient from this group revealed hypertrophy and dilatation affecting particularly the left ventricle.

In another group (Group II) the QRS sĚ-loops enclosed a narrow irregular area, and most of the subjects showed extreme cardiac enlargement and moderate to severe congestive heart failure. It is suggested that the pattern of the loops in this group is consequent to gross diffuse myocardial damage.

The QRS sĚ-loops of the subjects in Group III were characterized by extreme irregularities such as might be expected if a myocardial infarct were present. The clinical histories of three of these subjects were compatible with myocardial infarction.

Three subjects with minimal clinical evidence of cardiac disease presented QRS sĚ-loops which were similar in direction to those of normal subjects. One of these loops was also similar in contour to normal vectorcardiograms and at autopsy minimal evidence of cardiac disease was found.

This study offers suggestive evidence that spatial vectorcardiography may provide information relative to the cardiac status of patients with the electrocardiographic pattern of left bundle branch block which is not obtainable with conventional electrocardiograms.

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Anomalous Atrioventricular Excitation Produced by Catheterization of the Normal Human Heart

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During the withdrawal of a catheter-electrode through the right ventricle of 2 normal subjects the electrogram displayed briefly a short P-R interval and an aberrant QRS. In the simultaneously recorded standard lead, the phenomenon simulated what is seen in the Wolff-Parkinson-White syndrome. The findings are presented in support of the physiologic, rather than anatomic, explanation for anomalous atrioventricular excitation.

SODI-PALLARES and his associates[1] have reported on the nature of the intracardiac deflections when the standard electrocardiographic leads displayed the characteristics first described by Wolff, Parkinson, and White.[2] As part of the study they were able to produce records of a similar type in dogs. This was accomplished by tapping the upper portion of the interventricular septum with a probe which had been pushed through the free wall of the right ventricle. Following such manipulation there were, occasionally, runs of a rhythm characterized by a normal P wave, a short P-R interval, and an aberrant QRS with a slurred initial ventricular deflection (delta wave,[3] anomalous component[6]) not unlike that seen in anomalous atrioventricular excitation* in man.

In the course of a comprehensive study of the intracardiac potentials developed during electrical activity of the human heart, we have on two occasions while manipulating the catheter seen what appeared to be anomalous atrioventricular excitation in normal subjects. It is the purpose of this report to describe the records obtained.

CASE SUMMARIES

Patient QWI was a 45 year old Negro admitted to the hospital because of a convulsive seizure, the second since he sustained a fracture of the skull six months before admission. The course and laboratory data, including an electroencephalogram and x-ray examination of the skull, confirmed the clinical impression of post-traumatic epilepsy. Cardiac examination, including an electrocardiogram (fig. 1) and a teleroentgenogram, gave entirely negative findings. There was no history of paroxysmal tachycardia. Cardiac catheterization was performed one week after the last convulsion.

Patient PAQ was a 49 year old Filipino waiter, resident in the United States for twenty-two years, admitted to the hospital because of intermittent chills and fever of two weeks' duration. Two days after admission a low-grade fever subsided. The subsequent course and laboratory data favored a diagnosis of grippe. Cardiac examination, including an electrocardiogram (fig. 3) and teleroentgenogram, was productive of negative findings except for a soft

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* Since the electrocardiogram under consideration may occur without the other features of the syndrome described by Wolff, Parkinson, and White,[2] it is desirable to have some designation for it. Among those suggested have been: short P-R, bundle branch block syndrome,[4] pre-excitation,[5] and anomalous atrioventricular excitation.[6] The evidence against a block of a bundle branch being the mechanism responsible for the record seems convincing enough to make the first name undesirable. *Pre-excitation*[5] is a good term. It is brief, and embodies the concept of the mechanism involved without stating its specific nature. However, it fails to tell in what chamber the phenomenon is occurring, and whether the usual or other pathways of ventricular excitation are involved. *Anomalous atrioventricular excitation* is perhaps best, although the objection to this term is the fact that anomalous excitation of the kind it implies is usually, though not always,[4] limited to the ventricles or a part of them.[3] Despite this shortcoming it is believed to be the most desirable designation.

systolic murmur heard at the apex. There was no history of paroxysmal tachycardia. Although examination of the spinal fluid revealed no abnormality, serologic reactions for syphilis (Wassermann and Kahn) were positive. He was regarded as having late latent syphilis. Cardiac catheterization was performed one week after admission.

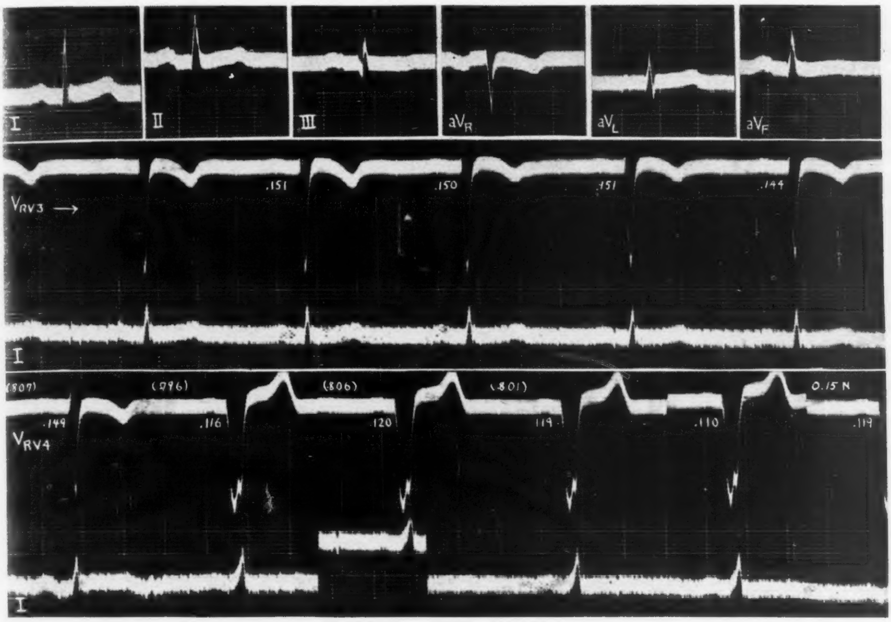

FIG. 1.—Electrocardiograms of Patient QWI. In the upper row are the standard leads (I, II, III), and the augmented extremity potentials (aV_R, aV_L, aV_F) recorded at normal sensitivity of the string (1 mv. = 1 cm.) The lower two rows are a continuous record of an intracardiac lead at 0.15 normal sensitivity made simultaneously with Lead I as the tip of the intracardiac catheter was slowly withdrawn from a point in the pulmonary conus (V_{RV3}) toward the lower part of the right ventricle near the apex (V_{RV4}) Withdrawal of the catheter was halted just before the standardization seen in Lead I of the lowest record. Just preceding this the shortening of the P-R interval (numbers under the intracardiac lead) and the considerable change in the QRS complex of both leads can be seen without significant change in the length of cycles (numbers in parentheses above the intracardiac lead). The new form continues to the end of the strip. Particularly to be noted is the slurred ascending limb of the R wave in Lead I, and the simultaneity of the peak of this deflection with the notch on the ascending limb of the aberrant QRS complex as well as with the nadir of the S wave of the earlier supraventricular complexes recorded from inside the heart.

The simultaneous Lead I is distorted by somatic tremors. Its smaller size, compared to the Lead I in the top row, is probably explained on the basis of increased resistance across this lead which developed as the electrode jelly dried in the course of the experiment. This tended to increase the relative size of the short circuit through the central terminal because a common electrode was used on each extremity. Time lines occur every 0.2 sec.

METHODS

Details of the methods will be reported elsewhere.[7] Briefly, two string galvanometers were used, one, with an amplifier in circuit, to record an intracardiac lead, the other to record in the usual way a lead somewhere from the surface of the body. The intracardiac exploring electrode was a solid woven catheter* with a silver cylinder, 3 mm. in length, at its distal end. The catheter was placed in the desired location by way of an antecubital vein, usually the left, under fluoroscopic observation.

Success in obtaining the records here reported was probably the result of our routine practice of

* Manufactured by the U. S. Catheter and Instrument Co., Glens Falls, N. Y.

making continuous tracings at any time that the catheter is being moved in the heart. In the first

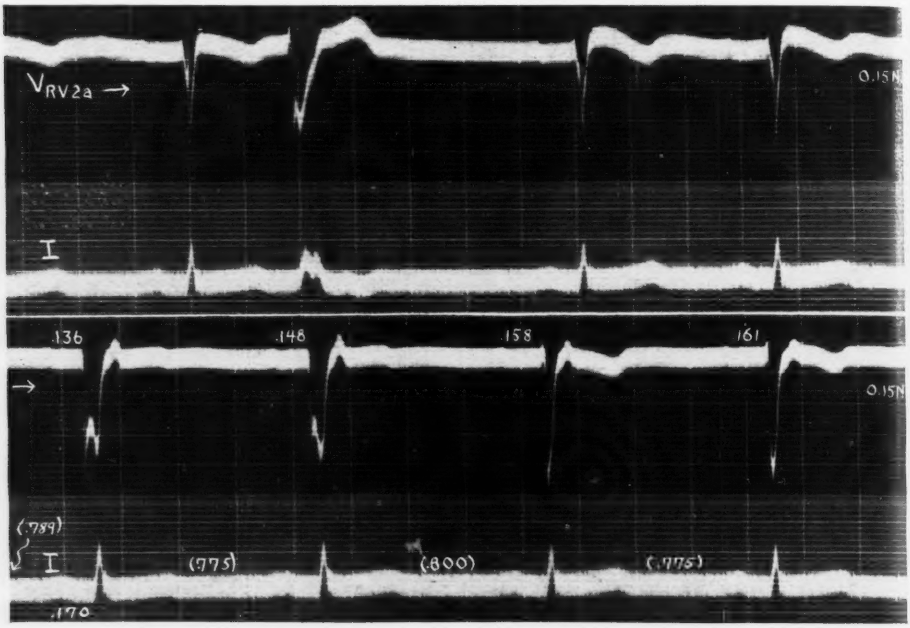

FIG. 2.—Patient QWI. Two strips taken from a continuous record made as the electrode was withdrawn from just below the pulmonary valve into the pulmonary conus. The upper string shadow in each row (V_{RV2A}) is the intracardiac lead at 0.15 normal sensitivity of the string. The lower is Lead I (I).

In the upper row there is a ventricular premature systole. Within the heart it begins with a small summit, presumably because its focus of origin was not at the tip of the catheter but at some more proximal (or distal) point. In later parts of the record (not shown) ventricular premature systoles occurred in which there was no initial summit. In this record the appearance of positive S-T displacement in systoles after the premature one is due to development of an injury potential from endocardial pressure of the electrode.

In the lower row, which begins four seconds after the end of the first, the injury potential on the intracardiac electrode has varied and given rise to a low, slurred summit just after the QRS complex of all four intracardiac complexes. The first two complexes in this row differ from the last two but in the simultaneous Lead I the corresponding ventricular deflections are the same in all four. Further, although the P-R interval is shortened within the heart (0.136 and 0.148 second), this is not evident in Lead I (0.170 second). The beginning of the large, intracardiac, ascending ventricular deflection (ascending limb of QS or S) is simultaneous with the peak of the R wave of Lead I in both types. In the first two complexes, then, the rapid initial downward deflection followed by smaller, slower waves in both directions preceding the peak of the R wave, together constitute the anomalous component or the delta wave (representing ventricular muscle excited anomalously from an ectopic focus at the tip of the electrode superimposed upon and obscuring the earliest deflections resulting from normal supraventricular excitation). Unlike what is seen in figure 1, the delta wave is not premature enough or of sufficient magnitude to be reflected in Lead I either by a shortening or distortion of the P-R interval or segment, or by a distortion of the QRS complex.[3] Further, this deflection varies somewhat in the first two intracardiac complexes as does the P-R interval. The numbers in parentheses above Lead I show the length of the cycles between beats.

patient (QWI), a short P–R interval and aberrant QRS complex developed on movement of the electrode from one location to another in the right ventricular cavity. Both locations were probably in the outflow tract of this chamber. In the second patient (PAQ), the change occurred while the tip was being moved from one point to another in the right pulmonary artery. It is likely that more proxi-

mal parts of the catheter, particularly those just below the pulmonary valve where the curvature of the catheter is usually sharper than elsewhere, made pressure on the ventricular wall to cause the abnormal electrocardiogram which resulted.

second and third lines labelled V_{RV3} and V_{RV4}. The lower record in these lines is the standard Lead I. The standardization in the latter on the lowest line indicates the point at which with-

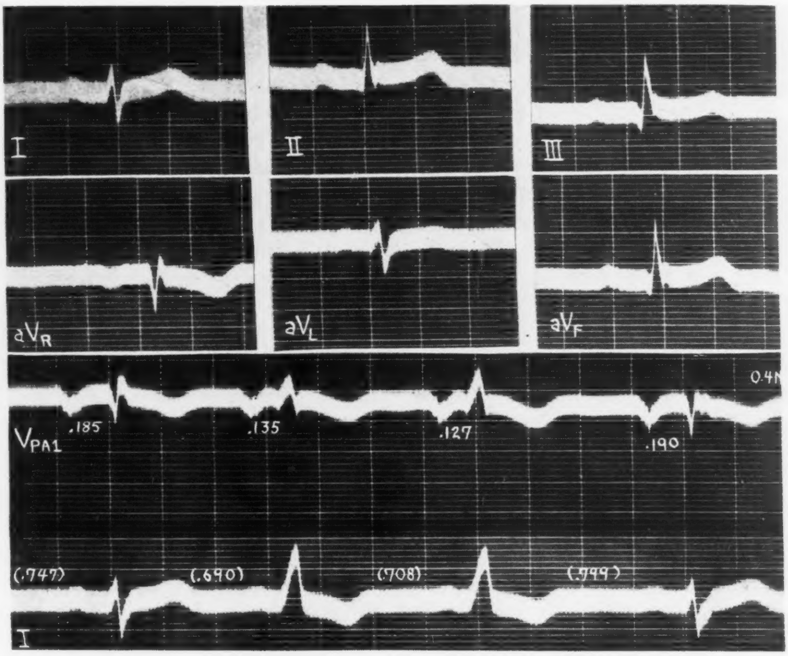

FIG. 3.—Electrocardiograms of Patient PAQ. The symbols have the same meaning as in figure 2. The lowest row is a record of the potential within the right pulmonary artery (V_{PA1}) recorded simultaneously with Lead I(I) as the intracardiac electrode was withdrawn slowly to a more proximal point in the right pulmonary artery. The numbers on the intravascular lead give the duration of the P-R intervals; the numbers in parentheses above Lead I give the duration of the cycle lengths. The shorter cycle lengths preceding the aberrant ventricular deflections were probably fortuitous, for they occurred elsewhere preceding normal ventricular complexes. Sensitivity of the string was normal for all but the intravascular records where it was 0.4 normal (0.4 N).

In the simultaneously recorded leads the appearance of the two middle QRS complexes preceded by shorter P-R intervals are to be noted. The P wave varies somewhat in the pulmonary artery, as is usual with movement of the electrode. No change is seen in this deflection in Lead I. It is believed that the QRS complex of the last cycle in both leads is slightly widened as a result of impaired conduction in the right bundle branch caused by pressure of the catheter. Subsequent ventricular deflections in the strip were similar to those of the first complex shown.

RESULTS

The intracardiac tracings, the standard leads, and the extremity potentials of the 2 patients are shown in figures 1 and 3. In the first (Patient QWI), the record obtained as the electrode was being withdrawn from the pulmonary conus to the lower part of the right ventricle near the apex is the upper tracing in the drawal of the intracardiac electrode was discontinued.

Just before withdrawal was halted, both the electrogram and the electrocardiogram changed considerably. In the former, the R wave was replaced by a deep, broad, negative deflection with a notch on its ascending limb simultaneous with the peak of R in Lead I. The RS-T seg-

ment became elevated and the T wave positive. This was in contrast to the normal intracardiac deflections in which the T wave was inverted, and the initial positive deflection, R, was gradually becoming larger and the S wave slightly shallower as the electrode was withdrawn. As might be expected in anomalous atrioventricular excitation, the S wave of the normal complex was not much altered, and could be identified as the notch on the ascending limb of the abnormal QRS complex. Also, as might be expected, the duration of the P-J interval* was the same in both types of systoles. In the simultaneous electrocardiogram (Lead I) the ascending limb of the R wave became slurred (anomalous component, delta wave), and the T wave almost isoelectric, simulating what is seen in the Wolff-Parkinson-White syndrome. The P-R interval, measured with greater accuracy in the electrogram, shortened from 0.149 second to 0.116 second, and was quite constant in all of the anomalous complexes. It also became shorter in Lead I. The P wave did not change. The cycle lengths with either type of ventricular excitation did not vary significantly or according to any recognizable pattern. The anomalous ventricular excitation persisted for twelve beats, at the end of which time recording was discontinued. When it was begun again, less than a minute later, the anomalous excitation had ceased.

Earlier in this experiment as the catheter was being withdrawn from one point to another in the conus itself the record shown in figure 2 was obtained. The upper intracardiac record in this figure shows simply a ventricular premature systole. The lower record differs from figure 1 in that the simultaneous standard Lead I does not show a delta wave even though the form of the initial parts of the intracardiac QRS complex in the first two complexes is quite different from the last, more normal two. Also, the P-R interval of the anomalous beats is slightly shorter than the normal in the lead from within the heart, and more so in the first (0.136 second) than in the second (0.148 second), but it is not shorter in the external lead.

* The interval measured from the beginning of the P wave to the junction of the QRS complex and the RS-T segment.

These data suggest that in this instance the myocardium excited anomalously was of such small extent that the phenomenon was not reflected in the QRS complex of Lead I. Even though ventricular excitation was slightly premature, no shortening of the P-R interval occurred in Lead I.

If one were to grade the three different types of anomalous beats shown, on the basis of the extent of the anomalously excited muscle, the completely aberrant record within the heart and in the standard lead (premature systole) would be first (fig. 2, upper record); the partially aberrant record found both within the heart and in Lead I would be second (fig. 1); and the aberrant record found within the heart but not in Lead I would be third (fig. 2, lower record). It would appear that prematurity of the ectopic beat, whatever its cause, was the factor responsible for the absence of or different nature of anomalous deflections when they occurred.

In the second patient (PAQ, fig. 3), the catheter was moved only a few centimeters while the tip was in the right pulmonary artery. At the end of this exploration it was still well to the right of the bifurcation of the pulmonary stem as determined on a frontal fluoroscopic projection. During the withdrawal, a record (V_{PA2}) was made simultaneously with Lead I (lowest line in fig. 3). In the figure the first beat may be regarded as the normal. The middle two are abnormal. In these the slurred ascending limb of R, the inverted T, and the short P-R interval in Lead I accompanied in the intravascular lead by a large, early, positive deflection rather than a late one, are easy to see. P waves are all the same in the standard lead but vary somewhat in the arterial lead as expected when the electrode is moved in the pulmonary artery.[7] Cycle lengths vary as shown by the numbers in parentheses above Lead I. Variations of this degree were found elsewhere in the record and were not considered to be significant.

The last QRS complex in this figure differs from the first in that it is wider and this widening affects principally the R wave in the pulmonic lead and the S deflection in Lead I. The T wave in the latter is also slightly taller than

in the normal control. The precise cause of these variations, seen in one other systole of the record, is unknown although impaired conduction through the right bundle branch produced for one beat by pressure of the catheter is a possibility.

Discussion

The data presented may be interpreted in one of three ways: (1) the catheter increased the rhythmicity of a center in the ventricular muscle which then fortuitously discharged at a rate similar to but preceding that of the sinoatrial node; (2) the catheter itself, extending as it does through the right atrium, was moved by contraction of this chamber to a sufficient degree to make more distal parts of it in the ventricle stimulate the latter prematurely, probably in the region of the upper right side of the interventricular septum; (3) the catheter increased the irritability of a ventricular center which was then discharged prematurely by atrial systole, either electrical or mechanical.

The first is unlikely because the cycle lengths preceding either a normal or an anomalous beat varied considerably (figs. 1 and 3). That an ectopic focus should discharge fortuitously under such circumstances just before and in relatively fixed relation to normal supraventricular excitation of the ventricles is not probable. The second is possible although the experimental observations on dogs[1] make it clear that a phenomenon similar to anomalous atrioventricular excitation may occur after the mechanical stimulus to the upper septum has been withdrawn. On the basis of this finding it is believed that the third interpretation, namely, an increase in irritability of a ventricular focus produced by the catheter, is most likely, and that the discharge of this center depends on either electrical or mechanical events in the atria.

Contraction of the atria as a stimulating factor seems a good possibility, since the "a" wave of the atrial sphygmogram in man begins on the average 0.09 second after the beginning of the P wave.[14] This causes a slight rise in intraventricular pressure which under certain circumstances of heightened irritability of the ectopic focus, such as could be caused by a foreign body (catheter) in the heart, may result in its premature discharge and the development of a short P-R interval and aberrant QRS complex. The time of discharge will depend in part upon the degree of irritability. All varieties of anomaly of the QRS complex, from a simple delta wave in direct leads with no change in the P-R interval or in the QRS complex of semidirect or indirect leads,[3] to considerable abbreviation of A-V conduction time and complete premature excitation of the ventricles from the ectopic focus,[15] are conceivable under such circumstances.

A question of considerably longer standing than these observations, is whether a mechanism similar to the one reported is responsible for the electrocardiogram seen in the Wolff-Parkinson-White syndrome. In the voluminous literature* which has appeared on this type of electrocardiogram, two principal mechanisms for its production have been suggested: one anatomic, the other physiologic. Among the anatomic tracts indicted have been: those similar to bundles described by Kent;[9] the paraspecific connections between the common bundle, the left bundle branch, and the upper septum as described by Mahaim and Winston;[10] and direct connections between the right atrium and the ventricular septum.[11] Since the papers by Holzmann and Scherf[8] and by Wolferth and Wood[12] appeared, suggesting an anatomic basis for the electrocardiogram and indeed for other features of the syndrome, a possible physiologic basis has been almost completely ignored.[4]

In retrospect, one of the fallacies of the anatomic concept has been to ascribe a function of conduction to a tract simply because it has been found to exist at necropsy in a patient known to have shown anomalous A-V excitation during life. It would appear that adequate attention has not been paid to control observations; it is not known what number of subjects will display such tracts at necropsy who never displayed the syndrome during life. If these should turn out to be numerous, and the observations of Glomset and Glomset[13] suggest that they are, the cause of the organic theory

* See the article by Segers, Lequime, and Denolin[3] and that by Öhnell[5] for a complete bibliography up to 1944.

should be seriously weakened. Further, and in addition to many other aspects, it is most difficult to explain on an anatomic basis the presence of the electrocardiographic features of the syndrome at times and their absence at others when the location and the rate of the pacemaker is constant.

Without giving all the pros and cons of the controversy,[4, 6] it seems just as easy to explain most of the features of the Wolff-Parkinson-White syndrome on the basis of an ectopic focus in the ventricles as on the basis of an accessory conducting pathway. It is also just as difficult to explain certain phenomena by the former as by the latter. The evidence presented here does not prove the one concept or disprove the other, but it should revive interest in the physiologic approach to the final solution of the problem.

Summary and Conclusions

1. In 2 patients with normal hearts, electrocardiograms with features usually ascribed to anomalous atrioventricular excitation were produced as an intracardiac electrode was slowly withdrawn through the right ventricle during a continuous electrocardiographic recording.

2. Contact of the catheter with the endocardial surface of the right ventricle resulted in increased irritability of a ventricular center most likely in the septum. During anomalous excitation of the ventricles this center was stimulated and discharged prematurely, possibly by the slight rise in intraventricular pressure ordinarily caused by atrial contraction.

3. The time of discharge of the new center determined the appearance of the simultaneous standard lead. When discharge was slightly premature, as determined from an early, minor, anomalous appearance of the QRS complex in the intracardiac lead, no change in one standard lead, and by inference in the other standard leads, could be seen.

4. Spontaneous physiologic alterations of a similar kind in a ventricular center would explain most of the features of the Wolff-Parkinson-White syndrome, without assuming the existence of one or more accessory anatomic pathways of conduction between the atria and the ventricles.

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Factors Influencing the Time of Appearance of Premature Systoles (Including a Demonstration of Cases with Ventricular Premature Systoles due to Re-entry but Exhibiting Variable Coupling)

By I. Mack, M.D., and R. Langendorf, M.D.

The genesis of the most common cardiac arrhythmia, that due to premature systoles, still remains obscure. Observations made upon two patients with ventricular premature systoles are reported because of some unusual features of their timing which shed some light upon the mechanism behind the appearance of premature systoles, regardless of the extrasystolic impulse. The theories of the extrasystolic irregularities are reviewed with particular attention to the criterion of "fixed coupling" generally used to distinguish between premature systoles explained by a re-entry mechanism and those explained by a parasystolic pacemaker.

In most studies of premature systoles the time of their appearance has been almost entirely ascribed to the mode of origin of the ectopic impulse. In fact, the distinction between the re-entry mechanism in cases of premature systoles with fixed coupling and parasystole in cases with varying coupling and with a common divisor of all interextrasystolic intervals was based primarily on such time relations. This article will attempt to demonstrate that variations in conduction of the premature impulse constitute another factor which determines the time of appearance of premature systoles; thus, in the 2 cases to be described, the premature systoles can be ascribed to a re-entry mechanism and their varying coupling explained by varying conduction. Rothberger emphasized that fixed coupling of premature systoles did not rule out the possibility of a parasystolic mechanism; our material is presented to demonstrate that varying coupling of premature systoles does not rule out the possibility of a re-entry mechanism.

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Mode of Origin of Premature Systoles

The genesis of premature systoles has been the subject of much study. Most observers now feel that premature systoles may arise in various ways.

The concept of parasystole as first suggested by Fleming,[1] and later stated definitely by Kaufmann and Rothberger,[2–4] has as its basis the idea that certain premature systoles were manifestations of an ectopic focus with a regular rate of impulse formation. Protection block (*Schutzblockierung*) was postulated to account for the fact that this ectopic center was apparently not penetrated by impulses of the dominant rhythm and discharged, with a disruption of its intrinsic rhythm.[2–4] The frequency and time of appearance of the premature systole were thought to depend on interference and dissociation between the two rhythms, on the presence of exit block (*Austrittsblockierung*),[5–7] and possibly also on some effect of the dominant rhythm on the "strength" of impulse formation in the ectopic focus.[5] Ventricular premature systoles which have been shown to be produced by such a mechanism

usually do not show fixed coupling with the dominant beats. Occasionally, however, fixed coupling may appear to be present when only a short strip of record is available because of a fortuitous relationship between the parasystolic rhythm and the dominant rhythm (e.g., when the cycle length of the dominant rhythm is almost an exact multiple or divisor of that of the ectopic rhythm). A parallel situation may be seen occasionally in complete auriculoventricular block in which the sinus nodal rate is almost exactly twice the idioventricular rate; short strips of record may then appear to demonstrate partial A-V block with 2:1 conduction, and only when a longer strip is examined is it seen that the two rhythms are almost completely independent.*

However, most premature systoles cannot be explained by the above concept since they usually demonstrate fixed coupling to the beats of the dominant rhythm, regardless of variations in this dominant rhythm. In such cases, most investigators are convinced that the impulse causing the premature systole is in some way itself caused by the beat that precedes it.[6, 9] The exact nature of this causal relationship is still poorly understood.

Many investigators have felt that the underlying mechanism for this type of premature systole is re-entry, and that the premature beat is actually caused by the same impulse which produced the beat of the dominant rhythm but which, because of a certain critical prolongation of the refractory period in some region of the heart, is able to re-enter the heart and so cause the premature systole. Attempts were first made to explain these premature systoles on the basis of a circus movement.[9–11] However, the fact that the coupling may be sometimes as long as 0.85 second [5, 6, 12] has been considered to be an important argument against this circus movement theory. For this reason, other investigators have suggested a broader concept of re-entry as a possible physiologic mechanism. They feel that in a certain region of the heart there may exist a critical prolongation of the refractory period so that the normal impulse, when it first arrives at this area, cannot penetrate or is not conducted through. When, however, very shortly afterwards the impulse reaches this area by another route, its refractory period will now be over and this impulse may then penetrate and be conducted through. In passing out of this area this impulse may now restimulate the rest of the heart provided the refractory period of the latter is now over.[6, 9, 13] In any discussion involving this region, the separate conception of protection block is unnecessary since the prolonged conduction assumed to be present in this region may tend to have the same effect as entry block.

Other observers, avoiding this concept of re-entry, believe that the premature systole originates as a new stimulus from an ectopic or heterogenetic focus which was in some way activated by the preceding beat. Scherf[14] experimentally, by injection of various drugs into the heart muscle, produced ventricular premature systoles of constant contour which showed fixed coupling to the preceding beats. That each premature systole was induced by the preceding sinus impulse was shown by the fact that the premature systoles disappeared when sinus standstill was produced by vagus stimulation. He believed that these premature systoles were not due to a re-entry mechanism, but were due to the formation of a new stimulus, because warming the area of injection increased the number of existing premature systoles or elicited premature systoles if tried shortly after they had disappeared. In earlier experiments,[15] when premature ventricular systoles produced in such a way followed not only the sinus beats but also artificially stimulated beats, he observed that these ventricular premature systoles retained their original contour. The coupling to the artificially stimulated beat would depend on where in the heart this artificially stimulated beat was produced, and whether or not either or both bundle branches

*Segers and associates[8] have shown that even during complete A–V block there may be some synchronization of auricular and ventricular rhythms, or frequent close association of a P and R wave (*phénomène d'accrochage*). They attributed this to interreactions developing between ventricles and auricles, without any conduction pathway, similar to the synchronization which may occur when two frog hearts are placed in contact with each other.

were intact. If the artificially stimulated beat arose in the opposite ventricle the coupling to the premature systole would be longer than when it arose in the same ventricle as the premature systole. The fact that the ventricular premature systoles retained their original contour, he felt, argued conclusively for the idea that these ventricular premature systoles arose from one sharply circumscribed area and this, according to him, spoke against re-entry.[15] However, if one postulates that the subepicardial injection of strophanthin, or digitoxin, produced a localized area of prolonged conductivity (as these drugs are known to do) where the re-entry phenomenon could occur, then certainly heating this area could have the effects he discovered. Because this area remained in the same location, the impulse coming out of this area would be conducted through the heart along the same pathway, and the form of the ventricular premature systole would thus remain constant.

Many of those who feel that premature systoles with fixed coupling originate in an ectopic focus believe that the activity of the ectopic center although continuous is raised to an effective level only when an impulse is conducted into it, or is completely inactive and develops a new impulse only when a stimulus penetrates it.[16] The idea of an ectopic center which rhythmically discharges subliminal impulses which are not effective, or cannot get out of the center, thus is not very far removed from the concept of parasystole. Indeed, cases have been reported in which the ventricular premature systoles were at first clearly parasystolic in origin, and in later records appear with fixed coupling,[17] and another reported in which ventricular premature systoles with fixed coupling and others due to parasystole were present in one record.[18]

It may well be asked: What happens to a sinus impulse which has activated the ectopic focus during the interval between the normal beat and the premature systole? If the length of the coupling interval is a measure of slow conduction out of the ectopic focus to the ventricle, then why is it necessary to postulate an ectopic focus, and how can we say the stimulus is one that has just been generated and not the same one that has re-entered the ventricle? Attempts to answer this question have been made by suggesting that it is not the sinus impulse itself that activates the ectopic center or makes possible the egress of the impulse from this center into the rest of the heart, but some condition produced by this sinus impulse which becomes effective only sometime after this sinus impulse has passed. Thus, Rothberger[5] mentions that the normal or dominant impulse may have an effect on the conduction out of the ectopic center similar to the *Bahnung* effect of von Skramlik (path-clearing effect of a nodal beat for subsequent A-V conduction[19]). Rothberger[5] also suggests the possibility that an impulse can come out of the ectopic center only during the supernormal phase of conductivity produced by the preceding sinus beat.[20–22] Segers emphasizes the role of the negative after-potential in the genesis of premature systoles, and he feels that the hyperexcitability after each contraction which coincides with the negative after-potential is responsible for the excitation to activity of an ectopic center. He found experimentally that drugs which diminish the negative after-potential lead to the disappearance of premature systoles (acetylcholine, quinidine, cocaine, procaine) and drugs which increase the negative after-potential increase the frequency of premature systoles (epinephrine, digitalis, strophanthin, veratrine, aconitine[23]). However, the presence of very long coupling (e.g., 0.85 second) cannot be explained by the above theories since the supernormal phase of recovery or the negative afterpotential usually does not appear so late in diastole.[20–22] The presence of long coupling, however, would not exclude the application of any of these factors to an area of prolonged conduction (where re-entry occurs), and where they could facilitate the entry or exit of an impulse.

The presence of this interval between the beat of the dominant rhythm and the premature systole has also been used as an argument against re-entry since during this interval there is no evidence in the electrocardiogram of the slowly traveling impulse in the re-entry pathway. However, a wave of excitation of narrow front and of very slow velocity will not register

in the electrocardiogram.[13] This can be seen in the portion of the electrocardiogram in which A-V conduction and conduction down the common bundle and bundle branches occur, and in which no sign of such activity can be detected.

Thus, in summary, it may be stated that most investigators agree that in the case of ventricular premature systoles with fixed coupling, the impulse of the dominant rhythm in some way causes the emission of another impulse from a relatively fixed focus. Whether this focus is an area in which conduction is prolonged so that re-entry becomes possible, or whether this focus actually becomes activated to initiate a new impulse cannot be answered definitely at this time.

Variable Conduction and Premature Systoles

In any attempt to determine the mechanism responsible for premature systoles in a given case, a consideration of the variations in coupling of the premature systoles to the dominant beats, and of the variations in intervals between the premature systoles, is of extreme importance. However, there is a factor influencing these critical time intervals which has been somewhat neglected in most discussions. The impulse which is responsible for the premature systole must be conducted along pathways in which variations of conduction will have a marked effect on these time relationships. Three possible regions may be considered where variations may occur in the conduction of the impulse which causes the premature systole: (1) In the pathway of the impulse of the dominant rhythm to the ectopic focus or to the region where re-entry occurs. (2) In the pathway from the point of exit from this ectopic focus or area of re-entry to the rest of the heart. This factor is important also in cases of parasystole. (3) In a region which is somewhere between the above two pathways, a region where there exists impaired conduction making the phenomenon of re-entry possible, namely, *the re-entry pathway itself*. All of the physiologic factors which influence conduction anywhere in the heart can affect conduction in any of these pathways.

If the rates of conduction along all of the pathways outlined above remain constant their existence will not interfere much with our attempts to understand the origin of the premature systoles in any given case. However, when such conduction delays become variable, the unravelling of the genesis of premature systoles in certain cases becomes very difficult. Thus, in a given case in which a regularly discharging parasystolic focus may be responsible for the premature systoles, the proof of such a mechanism may be greatly complicated or impossible, when the intervals between the premature systoles are affected by variable conduction in the second pathway described above; it will then be impossible to find a common divisor for the various intervals between the premature systoles. Such factors may be responsible for the variations in interextrasystolic intervals in the cases reported by Iliescu and Sebastiani.[9, 24] A similar situation holds in partial A-V block with the Wenckebach phenomenon and with dropped beats, in which, although the rate of discharge of the sinoauricular node is absolutely regular, the ventricular rate may be quite irregular because of varying A-V conduction (especially if conduction varies from 2:1, 3:2; 6:5, and so on).

Variable conduction in the pathways described may also lead to variable coupling of premature systoles to the preceding beat even when it can be shown that the latter is responsible for the former. We shall demonstrate two such cases with ventricular premature systoles, in which the variations in the coupling can be explained on the basis of variations in conduction in these pathways.

Case 1.—Figure 1 shows the limb leads of an electrocardiogram taken on a 25 year old man with rheumatic heart disease who was not receiving medication. Numerous interpolated ventricular premature systoles are present and exhibit variable coupling with the sinus beats. The spacing between the premature systoles appears to show some constant relation when compared in the various leads. However, slight variations in the sinus rate can be observed, and with them occur similar variations in the intervals between the premature systoles (e.g., in the intervals between the last three premature systoles in strip 3 in figure 1). This fact, plus some features even better illustrated in another record (fig. 3) taken on this patient, which will be shown

below, rule out the possibility of parasystole. The unusual feature of this record is the progressive lengthening of the coupling eventually leading to the omission of a ventricular premature systole. This is strongly reminiscent of the type of progressive conduction delay seen in partial A-V block with the Wenckebach phenomenon. Thus, somewhere in one of the pathways discussed above, there is partial could have the same effect. However, this conduction delay could also occur in the pathway from the ectopic focus, or from the area of re-entry to the rest of the heart. The fact that the length of the coupling appears to be inversely proportional to the interval between the preceding two beats would seem to indicate that the conduction delay is in either of these two pathways. However, in our

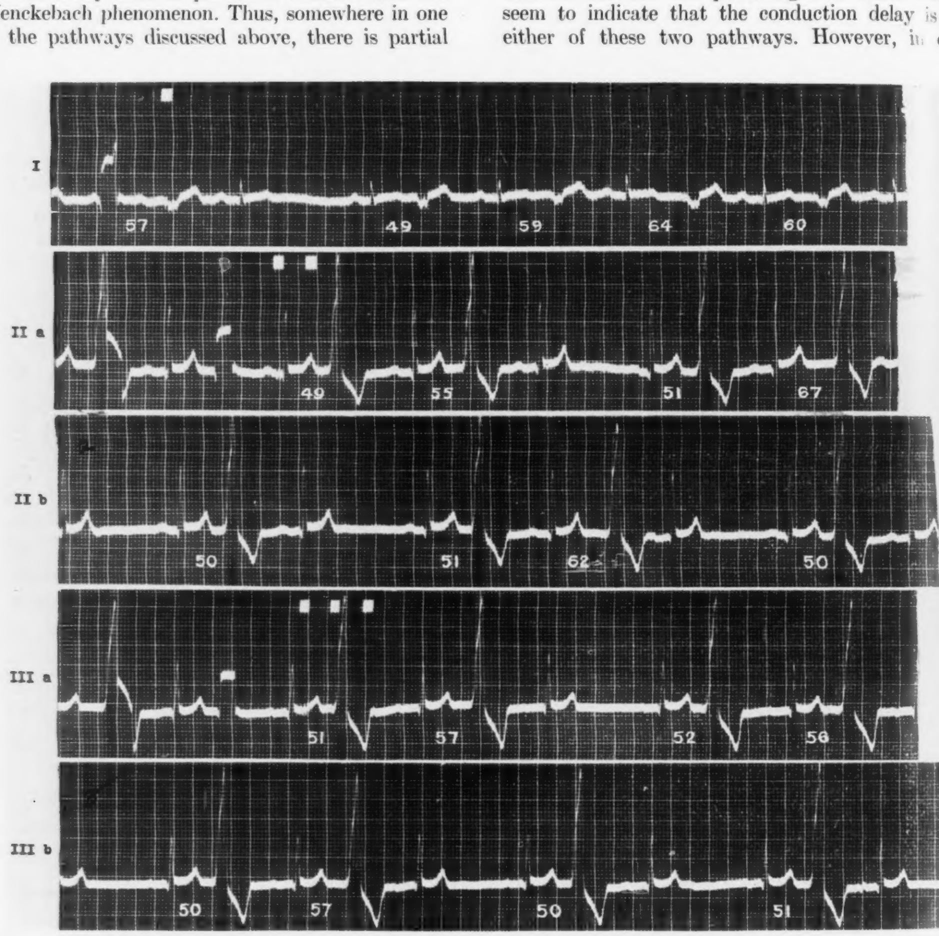

FIG. 1.—Case 1. Limb leads. Strip A and B of each lead are continuous. There are numerous ventricular premature systoles with progressive lengthening of coupling, leading to the omission of a ventricular premature systole. (Discussion in text.)

block with 3:2 conduction, since every third sinus impulse is not followed by a premature systole. Can this conduction delay be in the pathway of the sinus impulse to the ectopic focus or to the region where re-entry occurs? We know from animal experiments of Scherf[14,15] (see above) that changing the site of origin of the first beat may change its coupling with the premature systole that is caused by it. Then, certainly, variable conduction in such a pathway second case (figs. 4–6) the ventricular premature systoles are not interpolated, but are followed by a compensatory pause, so that this relationship does not hold. Furthermore, if either of these pathways shows variable conduction, then certainly it is not in the path of the main spread of the sinus impulse over the heart, since there is no aberrant conduction as evidenced by any changes in the contour of the sinus beat which immediately follows the premature

systole. It is therefore entirely possible that this progressive conduction delay with the Wenckebach phenomenon occurs in the re-entry pathway itself. The length of the coupling would then be related to the interval or the duration of the rest period between premature systoles. Such a relationship, present in this case, is also present in our second case.

In most of Lead 1 of Case 1, every sinus beat is followed by a ventricular premature systole, i.e., 1:1 conduction in one of the pathways just discussed. However, one unusual finding is the unexpected shortening of the coupling at the end of the strip systoles are present with persistent bigeminal rhythm. The increase in sinus rate was induced by amyl nitrite inhalation. The coupling is seen to remain rather constant, increasing slightly only towards the end of the strip as the intervals between the premature systoles become shorter, and as the intervals between the two beats preceding the premature systoles also become shorter. The increase in sinus rate combined with the slight prolongation of coupling results in the inscription of fusion complexes as seen towards the end of the record, indicated by "X." Fusion beats formed in such a way

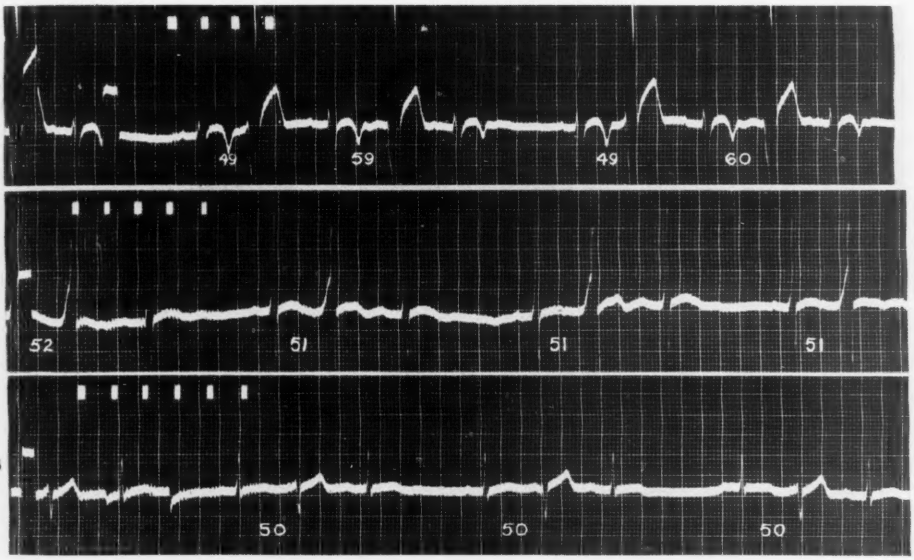

FIG. 2.—Case 1. Chest leads. In Leads CF_4 and CF_5 every other sinus beat is followed by an interpolated ventricular premature beat. (Discussion in text.)

without the dropping of a ventricular premature beat. This may be due to the fact that there is simultaneous slight slowing of the sinus rate with a consequent increase in the rest period between stimuli entering the region where re-entry occurs. However, it may also be considered as the same type of phenomenon sometimes seen in partial A-V block with the Wenckebach phenomenon when occasional shortening of the P-R interval occurs without the dropping of a beat.[5]

Figure 2 shows the chest leads in this same case taken immediately after the limb leads, and Leads CF_4 and CF_5 show the development of 2:1 conduction in one of the pathways described above, since every other sinus beat is followed by an interpolated ventricular premature systole.

Figure 3 shows a portion of a very long record taken on the same patient several days later where numerous noninterpolated ventricular premature are unusual. The relative consistency of the coupling in the face of such marked variation in the sinus rate rules out parasystole.

In examining long strips of the electrocardiogram in this patient it was noted that when the sinus rate was slow, every other sinus beat was followed by an interpolated ventricular premature systole. When the sinus rate became faster, bigeminal rhythm appeared, each conducted sinus impulse being followed by a noninterpolated ventricular premature systole, which was then followed by a nonconducted sinus impulse. Further increase in sinus rate leads to the disappearance of the ventricular premature systoles. All the phenomena described above could be found consistently in long strips of this patient.

The case described above is very similar to one reported by Zander[25] in 1927. He suggested

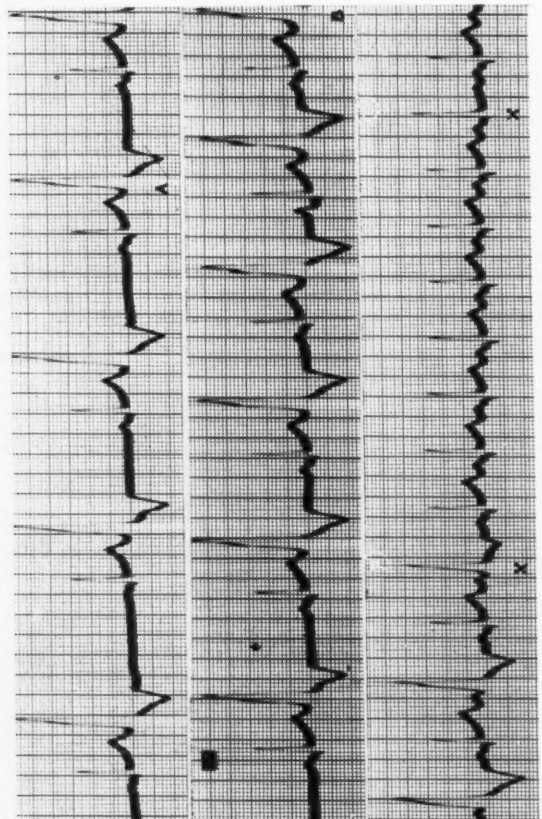

FIG. 3.—Case 1. Continuous record of Lead II. The end of each strip is reproduced again at the beginning of the strip just below it, identical beats being indicated by the same letter (A–A, B–B). Fusion complexes are marked "X." The gradual increase in sinus rate is produced by amyl nitrite inhalation. The coupling is seen to remain rather constant, increasing slightly only towards the end of the record. (Discussion in text.)

that there existed somewhere in the conduction system of the ventricles, a small portion in which conduction was so slow that by the time the sinus impulse passed through this portion, the absolute refractory period of the ventricles

variations in coupling were due not to variations in conduction but to variations in the rate of ectopic stimulus formation.

In an abstract submitted to the III Interamerican Cardiological Congress, Winternitz[26]

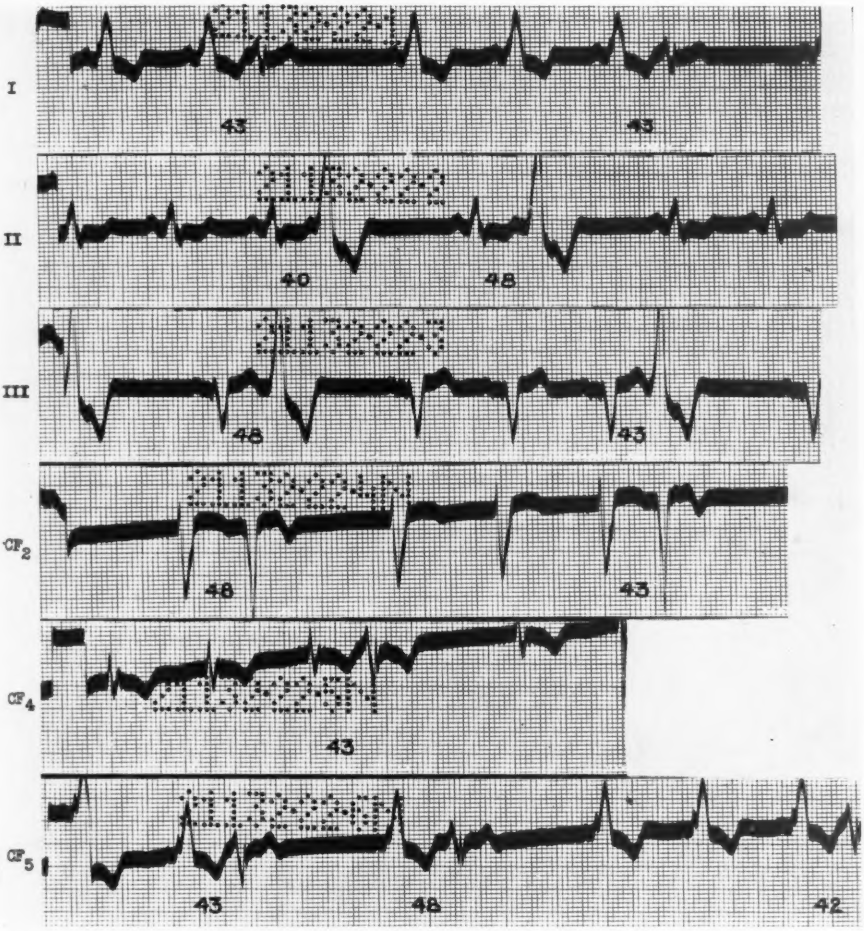

FIG. 4.—Case 2. Numerous noninterpolated ventricular premature systoles are present. (The variations in coupling are discussed in text.)

was over and they could again respond. He postulated 3:2 block with the Wenckebach phenomenon in this area. This explanation, when examined closely, is one which in essence also attributes the delay to the re-entry pathway. In 1928, Goldenberg and Scherf[12] also reported a case with similar features, but felt that the

called attention to disturbances in conduction of the extrasystolic impulse in cases of auricular fibrillation which showed premature systoles with fixed coupling occurring after digitalization. In his first case, showing bigeminal rhythm, the contour of the premature systole varies with the duration of the pause preceding

the conducted beat to which the premature systole is coupled. In his second case, showing intermittent bigeminal rhythm, the occurrence of premature systoles is demonstrated to depend on the duration of the pause preceding not receiving digitalis. Here again can be seen numerous ventricular premature systoles. Whenever two pairs of bigeminal beats follow one another, the coupling of the second pair is longer than the first. Here, however, in contradistinction to the first two records presented, the rest period preceding the pair

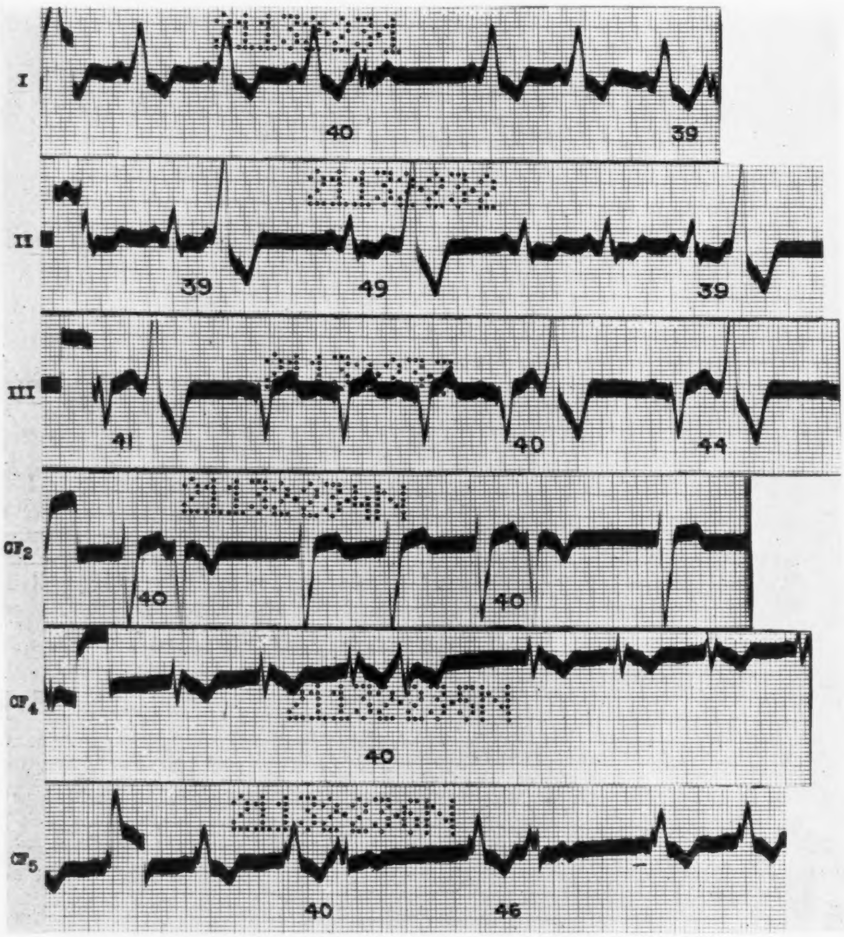

FIG. 5.—Case 2. Record taken one month after the one reproduced in figure 4. (Discussion in text.)

the conducted beat to which the premature systole is coupled. These phenomena are explained by Winternitz by a partial exit block for the extrasystolic impulse in the first case and by a complete exit block in the second case.

Case 2.—Figure 4 is a record taken on a 65 year old man with arteriosclerotic heart disease, who was of beats with the longer coupling appears longer than that before the pair with the shorter coupling because these premature systoles are not interpolated. It is, of course, possible that the sinus impulse which appears to be completely nonconducted may partially penetrate into an area in the ventricles near the ectopic focus, or near the area of reentry, before it is blocked and causes prolongation of the next coupling interval.[27] There is, however, no definite evidence that this occurs. Another possible

explanation would be that, since the cycle length preceding the second pair of beats is longer than that preceding the first pair of beats, the conduction in one of the discussed pathways is slower.[28] However, in figure 6 where the occurrence of a series of three and more bigeminal beats is shown, this factor will be seen not to be responsible. Thus, here again the important factor which appears to affect the coupling is the interval between the premature systoles, or in other words, the rest period in the re-entry pathway itself.

Figure 5 shows a record taken one month after the last one. The same phenomena are present.

Figure 6 shows a record taken seven months after the first one and here longer series of bigeminal beats are present in some of the leads. The shortening of the coupling towards the end of Lead III can be seen to be correlated with an increase in the interval between the premature systoles which in turn is caused by the slight slowing in sinus rate. That the progressive prolongation of coupling as seen in the last two figures was not due to the increased length of the preceding cycle can be seen also in this series of beats where the slight progressive prolongation of the cycle preceding each pair of coupled beats is nonetheless followed by shortening of the coupling. The ventricular premature systoles shown in figures 4, 5, and 6 are not due to parasystole since careful

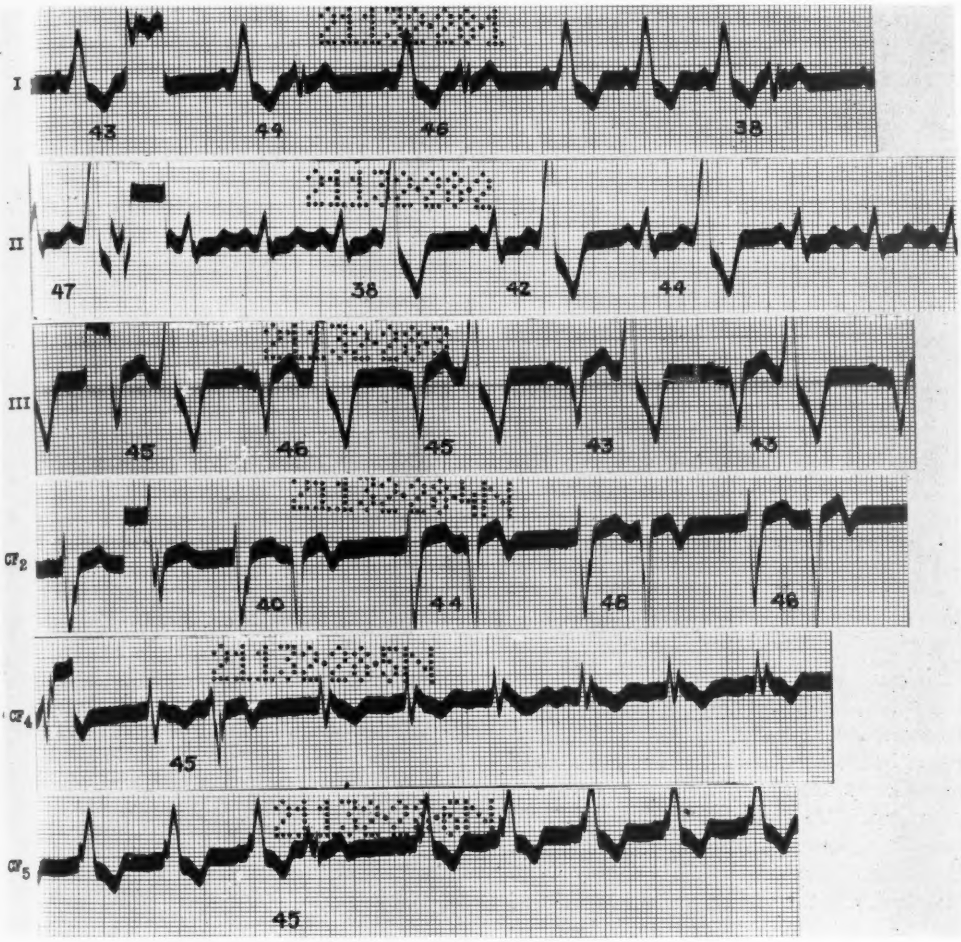

FIG. 6.—Case 2. Record taken seven months after the one reproduced in figure 4. (Discussion in text.)

mensuration shows the slight variation in the interextrasystolic intervals to be dependent on the equally slight variations in sinus rate.

We have thus demonstrated the importance of variable conduction in one of the three pathways described above in affecting the time of appearance of premature systoles of similar contour. It should also be emphasized that a similar mechanism may operate in some cases in which the contour of the premature systoles varies. This applies to instances with fixed coupling as well as to some with progressive lengthening of the coupling. Thus, differences in contour of premature systoles, while in most instances best explained by assuming that the premature beats arise from multiple foci, may conceivably also be the result of variations in the topographic pathways selected by the impulse, as determined by variations in refractory states of adjacent regions of myocardial tissue, in its course from the single ectopic focus or area of re-entry to the rest of the heart (i.e., aberrancy of conduction). In a similar way such variations in conduction of the extrasystolic impulse may be responsible for variations in rate and in contour in some cases of paroxysmal ventricular tachycardia.

Summary

The purpose of this paper has been to emphasize the importance of the hidden variations in conduction in pathways usually not considered in the determination of the genesis of premature systoles.

Three possible regions may be considered where variations may occur in the conduction of the impulse which causes the premature systoles: (1) In the pathway of the impulse of the dominant rhythm to an ectopic focus, or to the region where re-entry occurs; (2) in the pathways from the point of exit from a parasystolic focus, an ectopic focus, or an area of re-entry to the rest of the heart; (3) in a region which is somewhat between the above two pathways, a region where there exists impaired conduction making the phenomenon of re-entry possible, namely, the re-entry pathway itself.

The mechanism which in any given case may be responsible for premature systoles (parasystole, re-entry, and impulse formation by an ectopic focus) is discussed. It was suggested that variations in conduction in one or more of the above pathways could affect significantly the time of appearance of premature systoles owing to any of the above mechanisms. Thus, fixed coupling could not be considered a *conditio sine qua non* for the diagnosis of a reentry mechanism, and, similarly, parasystole cannot always be ruled out because of variations in the interextrasystolic intervals.

It was suggested that similar factors may be present in some cases in which the premature systoles have a variable contour, and in some cases of paroxysmal ventricular tachycardia with varying rate and complexes of varying contour.

It was demonstrated that while it may often be impossible to determine its exact site, the existence, at least, of such varying conduction could often be detected as in two cases with numerous ventricular premature systoles which were presented.

Acknowledgment

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Hypersensitive Carotid Sinus Reflex Associated with Spontaneous, Transient Complete Heart Block

By Irving L. Schwartz, M.D., and Ludwig W. Eichna, M.D.

A patient with transient, intermittent, complete heart block had periods of asystole, accompanied by syncope, whenever his cardiac rhythm shifted spontaneously from regular sinus rhythm to complete auriculoventricular dissociation. Similar clinical and electrocardiographic findings were produced by carotid sinus pressure when there was regular sinus rhythm. During the periods of heart block carotid sinus stimulation produced no effects. Physiologic studies suggested that the site of sensitivity of the hyperactive carotid sinus reflex was located at the effector end of the reflex arc. The possibility of structural damage to the heart from repeated stimulation of a hyperactive carotid sinus reflex is considered.

THIS IS a study of a patient with syncopal attacks due to ventricular arrest which, on occasion, were found to occur when the cardiac rhythm shifted spontaneously from normal sinus rhythm to complete heart block and which, on other occasions, followed stimulation of the right carotid sinus. The observations to be reported permitted an evaluation of the relative importance of the organic and neurogenic factors in the causation of these attacks and offered an opportunity to study the mechanism of transient heart block.

Case Report

The patient, a 73 year old Chinese man, was admitted to Bellevue Hospital following a fall in the street. He gave a one-month history of dizziness and fainting which had resulted in almost daily falls with consequent minor injuries. Unconsciousness usually lasted only a few seconds and was not related to head movement, neckwear, activity, or change of position. There were no aura, nausea, vomiting, tongue-biting, or incontinence of urine or feces. Chest pain, symptoms of diminished cardiac reserve, and previous heart disease or hypertension were denied. He did recall two episodes of palpitation during the three months prior to admission. System review and past history were otherwise noncontributory. The patient had been a heavy wine- and whiskey-drinker for many years but had entirely discontinued drinking alcoholic beverages two months before admission.

Physical examination showed a well-developed, well-preserved elderly Chinese man in no apparent distress. The rectal temperature was 98 F., respiratory rate 24 per minute, pulse rate 56 per minute, and blood pressure 200/90. There were bilateral arcus senilis, right periorbital swelling and edema, and a laceration 2 inches in length over the right eye. No abnormalities of the carotid arteries or adjacent tissues were noted. The heart sounds were distant; the aortic second sound was louder than the pulmonic; and a soft, medium-pitched, blowing systolic murmur was heard over the entire precordium, maximal in the third intercostal space at the left sternal border. The rhythm was regular with the ventricular rate equal to the pulse rate at 56 beats per minute, except for brief periods of five to seven seconds of irregular rhythm terminating in complete ventricular arrest, following which the heart resumed activity at a regular rate. The remainder of the physical and neurologic examination revealed no abnormality.

The urine was normal; its specific gravity was 1.015. Complete blood count showed: red blood cells —4,800,000 per cu. mm.; hemoglobin—12.9 grams per cent; white blood cells—9,250 per cu. mm. with a normal differential count. The Mazzini reaction was negative. Blood chemical analyses gave the following values: fasting blood sugar—81 mg. per 100 cc. of blood; calcium—12.4 mg. per 100 cc.; chlorides—528 mg. per 100 cc.; phosphorus—3.09 mg. per 100 cc.; albumin/globulin ratio—4.5/2.4; nonprotein nitrogen—34 mg. per 100 cubic centimeters. There were no parasites in the stool. The icteric index was 9. On lumbar puncture the initial pressure of the spinal fluid was 130 mm.; the Pandy reaction was negative; there were 900 red blood cells

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per cu. mm. of spinal fluid (traumatic tap); the Wassermann reaction was negative; and the colloidal gold curve read 112210000. Posteroanterior x-ray film of the chest showed the lungs clear and the heart not enlarged. Roentgenograms of the skull showed no abnormality.

Four days after admission while attempting to climb into bed the patient fell to the floor. The pulse rate was reported as 35 beats per minute with a rise to 60 beats per minute an hour later. Two days later, testing of the right carotid sinus reflex by digital pressure produced asystole and syncope fol-

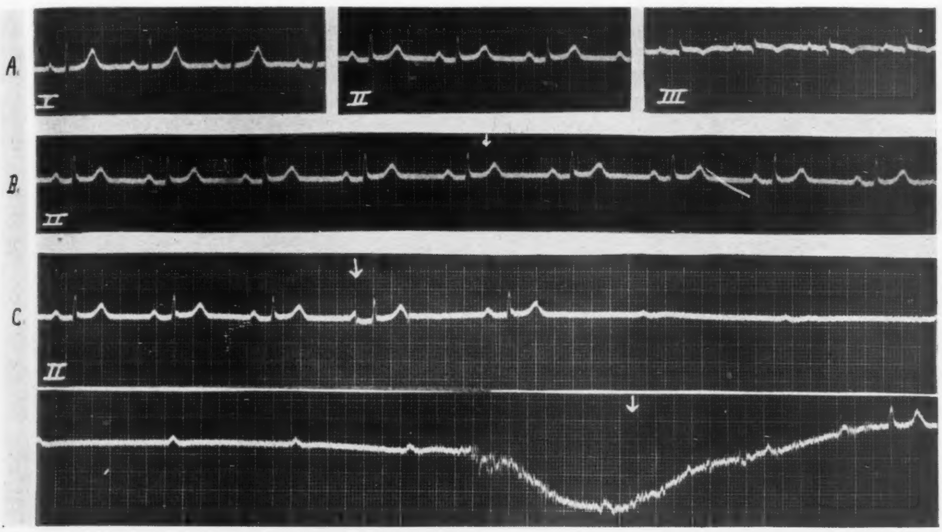


FIG. 1.—*A*, Control tracing, normal sinus rhythm. *B*, Left carotid sinus pressure with massage; arrow indicates release of pressure, which at this point had been maintained for twenty seconds. *C*, Right carotid sinus pressure with massage, ventricular asystole, and convulsion. Pressure was applied during the interval between the arrows. (The unlettered strip is continuous with the strip immediately above.)

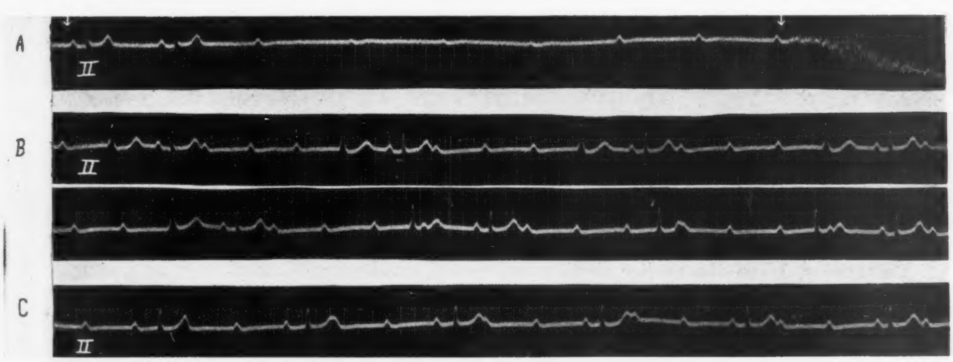


FIG. 2.—*A*, Normal sinus rhythm. Right carotid sinus pressure with massage, ventricular asystole, and convulsion. Pressure was applied during the interval between the arrows. *B*, Three minutes later. Periodic appearance of normally conducted beats of supraventricular origin indicates that, although A-V block was high grade, it was not complete. This probably represents the last vestige of normal A-V conduction. *C*, Ten minutes later. Stabilization in complete A-V block (compare with fig. 4, *C*). (The unlettered strip is continuous with the strip immediately above.)

lowed by a few convulsive movements (fig. 1, *C*). During the next few weeks the patient was observed to exhibit normal A-V conduction at times and complete heart block at other times. Spontaneous attacks of dizziness and syncope occurred. At this stage the nature of his cardiac rhythm and the cause of the syncopal attacks were not clear, and studies were undertaken to clarify the relationship between the carotid sinus reactivity and the spontaneously occurring heart block in the genesis of the syncopal attacks.

blocked (fig. 3, *B*), right carotid sinus pressure produced usually a slowing of the atrial rate of 10 to 15 beats per minute, and occasionally no effect. However, carotid sinus pressure on either side failed to produce ventricular asystole on any occasion, whether the atrium was slowed or not. The failure of the atrium to slow on a few occasions during right carotid sinus pressure cannot be explained; the pressure was applied always by the same observer who made every effort to keep the intensity, location, and duration of stimulation constant at all

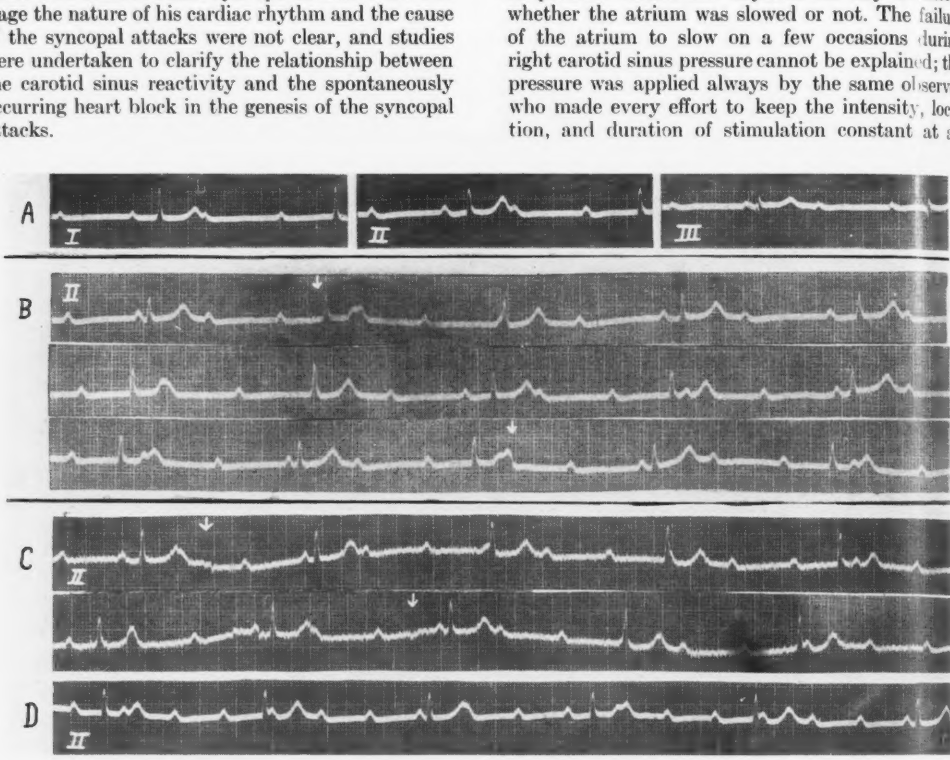


Fig. 3.—*A*, Control tracing, A-V block. *B*, Right carotid sinus pressure with massage applied during the interval between the arrows. Three seconds after the application of pressure the atrial rate decreased from 79 per minute to 66 per minute without alteration in ventricular rate. *C*, Atropine sulfate (2.0 mg.) injected intravenously during interval between the arrows. *D*, Thirty seconds after injection of atropine. (Each unlettered strip is continuous with the strip immediately above.)

Clinical Studies. When the cardiac rhythm and A-V conduction were normal, carotid sinus stimulation on several occasions gave the responses indicated in figures 1 and 2. Pressure on left carotid sinus produced a negligible response (fig. 1, *B*); but pressure over the right carotid sinus produced atrial slowing with change in the shape of the P waves and ventricular asystole which led to a convulsion (fig. 1, *C*). The ventricular asystole produced by right carotid sinus stimulation was followed by a high-grade, but not complete, A-V block (fig. 2, *B*). Approximately ten to thirty minutes later this rhythm changed to that of complete A-V block (fig. 2, *C*).

In contrast, whenever A-V conduction was times. During these observations, both with and without A-V block, the blood pressure ranged from 90–144/40–62; and at no time did carotid sinus stimulation produce a primary depressor response.

The demonstration of carotid sinus hypersensitivity during periods of normal sinus rhythm but not during periods of A-V block is to be anticipated, since a neurogenic (vagal) effect, which is manifested by a sudden interruption of A-V conduction, is not to be expected when A-V conduction is already blocked.

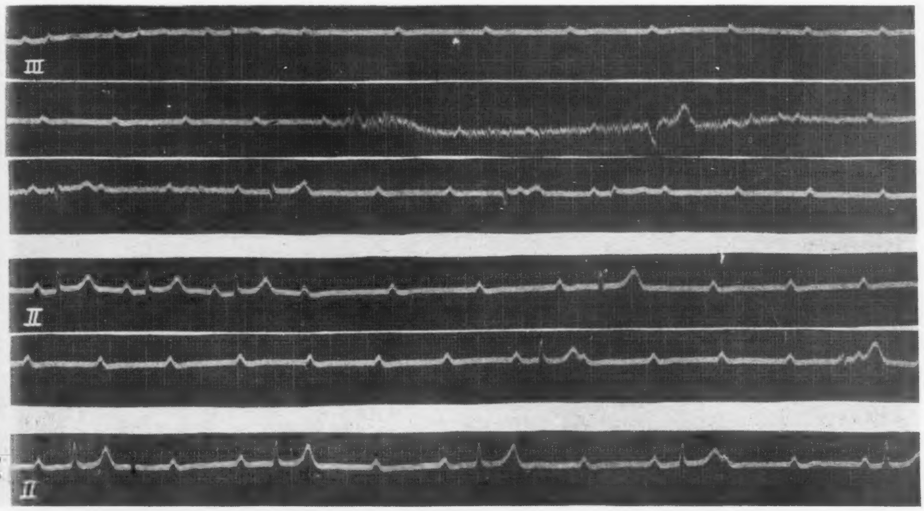
On several occasions the patient was observed in a period of spontaneously shifting rhythms. At these times complete A-V block predominated with a ventricular rate of 34 beats per minute. Every five

to ten minutes there was a temporary restoration of A-V conduction and normal sinus rhythm ensued with a ventricular rate of 60 beats per minute. After one to three minutes of the normal sinus rhythm a spontaneous ventricular arrest of three to ten or more seconds occurred, following which there was reactivation of an idioventricular center with complete A-V block (fig. 4). During the asystole the patient became pale, and if the asystole was prolonged, he had a mild generalized convulsion. On recovery of consciousness he was momentarily confused. A-V block then continued until normal conduction was resumed spontaneously, and the cycle repeated. Such a change in conduction occurred approximately three or four times in the half hour that he was observed before his rhythm became stabilized in A-V block. These attacks were all spontaneous; the patient lay supine in bed with his face directly upwards. There was no turning of the head preceding an attack. After the asystole there was a period of incomplete A-V block with occasional normal conduction of supraventricular beats. This rhythm gradually yielded to complete A-V block. Thus the events following spontaneous ventricular asystole were the same as after ventricular asystole induced by right carotid sinus stimulation (compare figs. 4, *C* and 2, *C*).

It was now considered that the patient's spontaneous syncopal attacks were more likely the result of ventricular arrest associated with the spontaneous changes in A-V conduction than the result of a hypersensitive carotid sinus reflex.

Several studies made during complete A-V block pointed to an organic rather than functional basis for the block. Normal A-V conduction could not be restored by any of the following procedures: (1) The administration of 2 mg. atropine sulfate intravenously increased the atrial rate briefly from 88 beats per minute to 114 beats per minute, and the idioventricular rate from 31 beats per minute to 34 beats per minute, but did not alter the A-V block (fig. 3, *C*). (2) The right carotid sinus was blocked with 10 cc. of 1.5 per cent procaine; a mass block was effected and produced hoarseness and Horner's syndrome on the right side but did not affect the ventricular rate or A-V conduction. (3) Inhalation of 100 per cent oxygen flowing continuously at 6 liters per minute failed to affect the complete A-V block.

A



B

C

FIG. 4.—Spontaneously changing cardiac rhythm. Tracings taken with the patient lying flat in bed without movement. *A*, Ventricular asystole followed by convulsion. *B*, Ventricular asystole is not prolonged enough to produce a convulsion. *C*, Stabilization in complete A-V block (compare with Fig. 2, *C*). (Each unlettered strip is continuous with the strip immediately above.)

In view of the carotid sinus hypersensitivity demonstrated by applying digital pressure from without, an attempt was made to stimulate the carotid sinus from within by elevating the arterial pressure. The cold pressor test was chosen for this purpose. On two separate occasions, when A-V conduction was normal, immersion of the forearm in ice water produced a marked rise in blood pressure from 134/74 to 202/92 and from 104/58 to 204/102. On each occasion, as the blood pressure reached its peak, ventricular asystole occurred (fig. 5, *A*). On one occasion, following the ventricular asystole, normal

A-V conduction was resumed immediately. Then, after removal of the forearm from the cold water, there followed a period during which the blood pressure fluctuated widely. Ventricular asystole occurred whenever the blood pressure became elevated above 160/80 (fig. 5, *B*); but as the blood pressure fell below this level, normal A-V conduction returned. On the other occasion ventricular asystole was followed by a period of A-V block before A-V conduction returned and normal sinus rhythm again ensued. Again there followed a period during which the blood pressure fell irregularly with occasional spikes above 160–80; and again ventricular asystole occurred whenever the blood pressure became elevated. When the blood pressure stabilized at its initial level, A-V conduction returned and normal sinus rhythm was re-established.

These asystolic episodes cannot be attributed unequivocally to carotid sinus stimulation by the increased arterial pressure, because of the possibility that they could have been due to decreased circulation to the A-V bundle during the pressor test. An attempt to decide between these two alternatives by repeating the cold pressor test after abolishing vagal influence was unsuccessful because on this occasion complete A-V block occurred immediately after 2.5 mg. atropine sulfate were injected intravenously.

Course. After a number of spontaneous Adams-Stokes attacks the patient stabilized in heart block. Novatropine (0.005 Gm., four times a day) and atropine sulfate (0.0004 Gm., four times a day), were given by mouth. Atropine was increased to tolerance in the hope of breaking the A-V block, but without success. Heart block with a ventricular rate of 34 beats per minute became established and the patient was discharged to be followed in the outpatient cardiac clinic.

During his repeated visits to the clinic complete A-V block was usually observed. However, on three visits normal sinus rhythm with rates of 60 to 66 beats per minute was noted. On one occasion he complained of attacks of dizziness but denied fainting or unconsciousness. The next morning an electrocardiogram was made; this revealed the same spontaneously changing A-V conduction that had been noted four months previously. For the next two years (May 1947 to June 1949) the patient visited the clinic at frequent intervals and on all occasions he was observed to have complete A-V block with a ventricular rate of 32 to 40 beats per minute. During this period he has been free of Adams-Stokes seizures. Cardiac reserve and general condition appear about the same as two and one-half years previously when he was first admitted to the hospital.

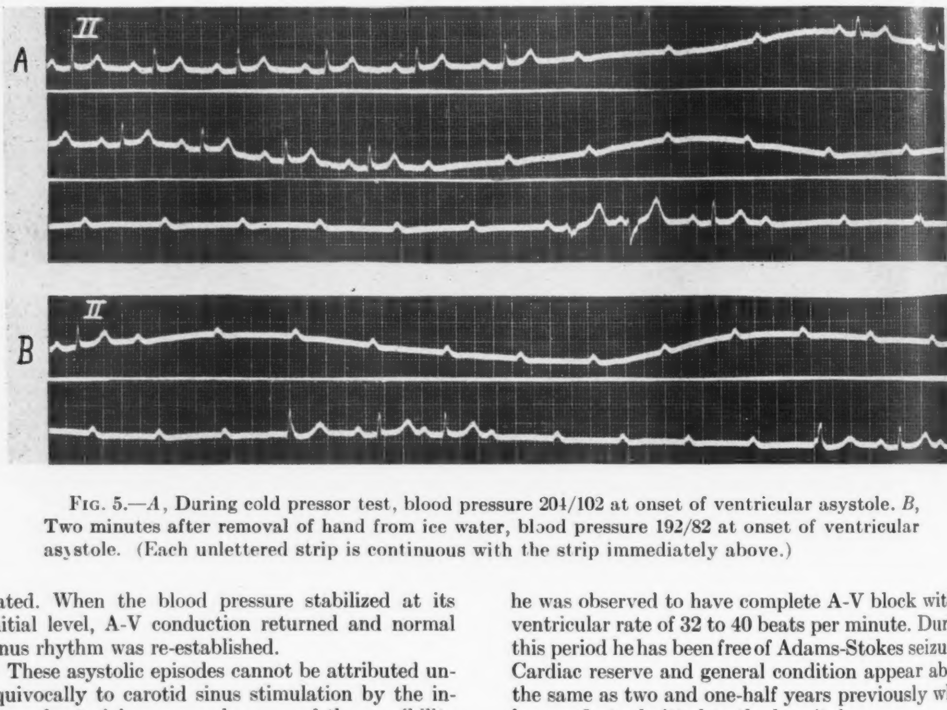


FIG. 5.—*A*, During cold pressor test, blood pressure 204/102 at onset of ventricular asystole. *B*, Two minutes after removal of hand from ice water, blood pressure 192/82 at onset of ventricular asystole. (Each unlettered strip is continuous with the strip immediately above.)

DISCUSSION

Transient Heart Block. Complete heart block alternating with normal conduction is a relatively infrequent occurrence. In 1934 Weiss and Ferris[1] reported two cases of transient complete heart block in association with the Adams-Stokes syndrome and cited only fourteen other cases in the previous literature, including those collected by Carter and Dieuaide[2] in 1923. In the more recent literature, transient complete

heart block has been reported in association with congenital heart disease[3, 4] and as a result of the acute myocarditis of rheumatic fever,[5] diphtheria,[6] mumps,[7] and scarlet fever.[8]

Unique cases of congenital heart block with transitory periods of normal sinus rhythm were described by Smith[9] and by Calandre.[10] Smith's patient had complete heart block which was unaffected by exercise or atropinization, but A-V conduction could be restored with a return to normal sinus rhythm by forced expiration. The author suggested that this change might be explained mechanically by lessening of traction on the conduction system owing to the altered position of the heart during forced expiration. Calandre's patient also exhibited complete heart block, except when in absolute repose at which time conduction was normal.

In most cases the transient heart block ultimately changed to permanent heart block and postmortem examination revealed underlying anatomic lesions within the cardiac conduction system. In a few cases of transient heart block, evidence of a neurogenic origin was present; and in this group Weiss and Ferris included their own three cases of vagovagal reflex Adams-Stokes syndrome,[1] the similar cases of Flaum and Klima,[11] and of Gluch,[12] and the cases due to hyperactivity of the carotid sinus.[13] Our patient belongs with that group of cases[14-18] with anatomic lesions which incompletely sever the cardiac conduction system and in which a sudden increase in vagal tonus precipitates the development of complete A-V block.

Site of Hypersensitivity of the Hypersensitive Carotid Sinus Reflex. The site of hypersensitivity of a hyperactive carotid sinus reflex may be in the afferent nerve endings of the sinus, in the medullary synapses of the central nervous system, or in the efferent nerve endings such as the vagal endings in the heart, alone or in combination. Observations[13, 19-21] in cases with local abnormalities of the carotid artery and adjacent tissues on the side of a hypersensitive reflex suggested that the hypersensitive carotid sinus reflex results from a pathologic lesion within or impinging upon the sinus itself. On the other hand, there has accumulated clinical,[22a, 22b, 23, 24] experimental,[25] and morphologic[26] evidence in favor of the view that the site of hypersensitivity in the "vagal" or cardioinhibitory type of reflex is predominantly, if not entirely, at the effector end of the reflex arc. The observations in the patient here reported may be interpreted in support of this viewpoint. The persistence of P waves (at a rate never less than forty-four per minute) throughout ventricular asystole indicates that potential stimuli for ventricular contraction were present during asystole but were blocked in propagation to the ventricle. This suggests that the site of carotid sinus hypersensitivity in this patient was located primarily in the vicinity of the A-V node and bundle, which coincides with the site of the lesion as inferred from the later development of permanent A-V block.

Permanent A-V Block Precipitated by Carotid Sinus Pressure. The development of permanent A-V block in this patient raises the question of structural damage to the heart as a consequence of carotid sinus sensitivity. Such reports have not been found in the literature, although cerebral damage following carotid sinus stimulation has been observed.[27-30] There is clinical and experimental evidence[31-35] that the coronary circulation and myocardium may be adversely affected by the carotid sinus reflex. Glenn and Read[31] reported a case of coronary artery disease in which anginal pain, similar to the patient's spontaneous symptoms, could be reproduced by carotid sinus stimulation. Friedman[32] observed two young adults without cardiovascular disease in whom anginal pain occurred following carotid sinus stimulation but not following severe exertion. Stella[34] observed a decreased coronary blood flow following elevation of pressure within the perfused carotid sinus of a dog's heart-lung-head preparation. Hall, Ettinger, and Banting[35] reported that repeated intravenous infusions of acetylcholine produced myocardial damage, and that vagal stimulation alone could cause myocardial degeneration, small infarcts, and electrocardiographic changes.

This evidence is indirect, but nevertheless indicates the possibility that stimulation of the hyperactive carotid sinus reflex may result in some subtle structural alteration in addition to the transient dramatic asystole. Such altera-

tion would escape clinical detection unless it involved a critical area such as the cardiac conduction system. The absence of clinical symptoms in the patient here reported until shortly before his hospital admission reflects "the large reserve in the conducting capacity of the A-V bundle, which structure may be considerably encroached upon before conduction is measurably impaired. Thus, with only a few intact fibers serving to carry on the normal conduction process, an increase in vagal activity and/or a small local decrease in circulation may result in failure of these few remaining fibers to function."[2] Such a loss of function would result in permanent A-V block if the anatomic lesion were extended through these last intact fibers. It is at least possible that in the patient here studied some such progressing change may have resulted from repeated stimulation of his hypersensitive carotid sinus reflex. As a consequence the remaining few intact fibers of the A-V conduction system may have been obliterated with the result that the initially transient complete heart block became permanent.

It is a matter of pure speculation whether repeated carotid sinus stimulation hastened the establishment of permanent heart block in this case, or whether the block resulted from the natural progress of the primary disease. Nevertheless, whatever its cause, the development of permanent block was beneficial to the patient. With this conduction system precariously near the point of complete severance, he was imminently susceptible to the onset of complete A-V block and ventricular standstill; but with the establishment of permanent A-V block with an idioventricular rhythm, the pacemaker of which was located below the site of vagal susceptibility, he was freed from his asystolic episodes and syncopal attacks. This change would have been valueless if the idioventricular focus were prone to retardation or to periods of complete inactivity. In this patient the complete A-V block, with an idioventricular rhythm at a rate of 32 to 40 beats per minute, has been present for two years during which he has been active and free of symptoms. In this sense the development of permanent heart block has been of benefit to him.

Summary

1. A case of transient complete heart block is described in which there were present a hyperactive cardioinhibitory carotid sinus reflex and a probable organic lesion of the A-V conduction system.

2. During periods of A-V conduction with normal sinus rhythm, carotid sinus stimulation produced asystole; during periods of complete A-V block, carotid sinus stimulation was without effect.

3. Several clinical studies indicated that the region of the anatomic lesion (vagus endings or His bundle) represented the site of greatest sensitivity of the hyperactive reflex in this patient.

Acknowledgment

The authors wish to thank Mr. William H. Becker for his helpful technical assistance in this study.

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Auriculoventricular Nodal Escape in the Presence of Auricular Fibrillation

By W. Hwang, M.D., and R. Langendorf, M.D.

The criteria for the diagnosis of A-V nodal escape are analyzed on the basis of electrocardiograms on patients with auricular fibrillation with digitalis-induced ventricular slowing.

IN THE presence of sinus rhythm the electrocardiographic diagnosis of A-V nodal escape is based on the delayed occurrence of a ventricular complex associated either with the absence of the sinus P wave preceding the late ventricular complex, or its presence with an abnormally short P-R interval. Obviously, in the presence of auricular fibrillation the lack of P waves makes the second criterion inapplicable and the identification of an A-V nodal escape becomes more difficult and less certain. Only occasionally, slight aberrancy of ventricular conduction helps to identify the beats of A-V nodal origin. On the basis of the single criterion of the long R-R interval, A-V nodal escapes should be recognizable in the presence of auricular fibrillation as beats which terminate long R-R intervals provided the latter are of equal duration and the longest in the record (fig. 2, *A*). A study of the exceptions to this rule is the main subject of this report which is based upon an analysis of twenty-five records obtained on 16 patients with auricular fibrillation and with sufficient material to permit a definite diagnosis of A-V nodal escape.

The outstanding clinical and electrocardiographic findings are summarized in table 1.

Method and Results

Clinical Diagnosis. The electrocardiograms were obtained on 8 men and 8 women patients between the ages of 18 and 80 years. The clinical diagnosis was combined arteriosclerotic and hypertensive heart disease in 7 patients, chronic rheumatic heart disease in 8, and chronic rheumatic heart disease complicated by hyperthyroidism in one.

Digitalis Effect. All the patients were under the influence of digitalis medication and this was undoubtedly responsible for the slow ventricular rate and the appearance of A-V nodal escapes. When previous or subsequent records were available for comparison they showed invariably absence of nodal escapes with increase of the average ventricular rate. In the twenty-five records with A-V nodal escapes the average ventricular rate varied between 45 and 80 per minute, with an average of 57 for the entire series. In fourteen records the average ventricular rate was 55 per minute or less. In twelve of the records the ST-T complexes showed a characteristic digitalis contour. In six records ventricular premature systoles were present. Clinical signs or symptoms of digitalis intoxication were absent in the entire series.

Inherent Rate of the A-V Node. The rate of the secondary pacemaker as determined by the duration of the escape intervals (2.20 to 1.12 seconds) was between 27 and 54 per minute with an average rate of 42 for all cases. It is of interest that, in one patient studied, the A-V nodal rate remained remarkably constant over a period of twelve years.

Varying Contour of the A-V Nodal Escape. In one case only was the contour of the nodal escape different from that of the transmitted beats (fig. 2, *B*). This was attributed to aberrant ventricular conduction rather than to escape of an idioventricular pacemaker located below the bifurcation of the common bundle.

Variation of the Escape Intervals. Analogy with the phenomenon observed in patients with sinus rhythm helps to explain why some escape intervals may be shorter, others longer, and on

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occasion an escape may fail to appear so that the beat terminating an unusually long pause may be a conducted one.

"warming up" of the secondary pacemaker (Gaskell's[1] rhythm of development) (see fig. 1, *A* and fig. 3).

TABLE 1.—*Summary of Pertinent Data*

Case No.	ECG No.	Age	Sex	Average Ventricular Rate	Nodal Escape		Digitalis		Clinical Diagnosis	ECG Diagnosis	Illustrated in
					R-R Interval in sec.	Rate/min.	S-T-T	P.V.S.			
1	5	73	M	55	1.58	38	yes	no	Ascl. H.D.; Hypt. H.D.	L.H.S.	Fig. 2,*B*
2	1	49	F	75	1.26	48	no	no	Rh. H.D. with	C.C.I.	
	2	49	F	52	1.72	35	no	yes	failure		
3	9	36	M	46	1.60	37	no	no	Hyperthyroid-	L.A.S.	Fig. 3
	10			50	1.46	41	no	no	ism; Rh. H.D.		
	11			45	1.70	35	no	no	in failure		
4	6	29	M	46	2.20	27	no	no	Rh. H.D.; Polyserositis	Low voltage	
5	2	63	M	70	1.36	44	yes	yes	Hypt. H.D. in failure	L.H.S.	
6	10	48	F	80	1.32	45	yes	yes	Hypt. H.D.; C.C.I.	L.H.S.; C.C.I.	
7	1	55	F	58	1.44	42	yes	yes	Rh. H.D. in failure	L.H.S.	
8	2	68	M	45	1.76	34	yes	yes	Ascl. H.D.	L.H.S.	Fig. 2,*A*
	3	68	M	50	1.66	36	yes	yes			
9	1	79	F	50	1.32	45	?	no	Ascl. H.D.	Left B.B.S. block	
10	1	18	F	70	1.12	54	no	no	Rh. H.D.	R.H.S.	
	4	21		60	1.12	54	no	no			
	5	22		70	1.12	54	no	no			
	10	27		66	1.12	54	no	no			
	11	30		54	1.12	54	yes	no			
11	2	44	F	62	1.46	41	yes	no	Rh. H.D. ? S.B.E.	R.H.S.	
12	6	62	F	50	1.80	33	yes	no	Rh. H.D. pul. embl.	R.H.S.	
13	3	58	M	53	1.14	53	no	no	Rh. H.D.	C.C.I.	Fig. 4
14	1	72	M	54	1.25	48	yes	no	Ascl. H.D.; myo-	Nonspecific ab-	
	2			48	1.35	44	yes	no	cardial infarction	normality	
15	1	42	M	60	1.36	44	yes	no	Rh. H.D.	Nonspecific abnormality	
16	4	80	F	58	1.36	44	?	yes	Ascl. H.D.	Right B.B.S. block	
Average		18–80		57	1.43	42					

Ascl. H.D. = arteriosclerotic heart disease; Hypt. H.D. = hypertensive heart disease; Rh. H.D. = rheumatic heart disease; S.B.E. = subacute bacterial endocarditis; Pul. embl. = pulmonary embolism; C.C.I. = chronic coronary insufficiency; L.H.S. = left heart strain; L.A.S. = left axis shift; Left or right B.B.S. block = left or right bundle branch system block; P.V.S. = premature ventricular systole.

The cause for these variations includes the following:

1. If several escapes occur in succession the first escape interval may be slightly longer than the subsequent ones as a result of a gradual "warming up" of the secondary pacemaker (Gaskell's[1] rhythm of development) (see fig. 1, *A* and fig. 3).

2. The first escape interval may appear shortened as a result of a delay in A-V conduction below the site of the secondary pacemaker affecting the conducted beat preceding the escape (Scherf[2]) (see fig. 1, *B*).

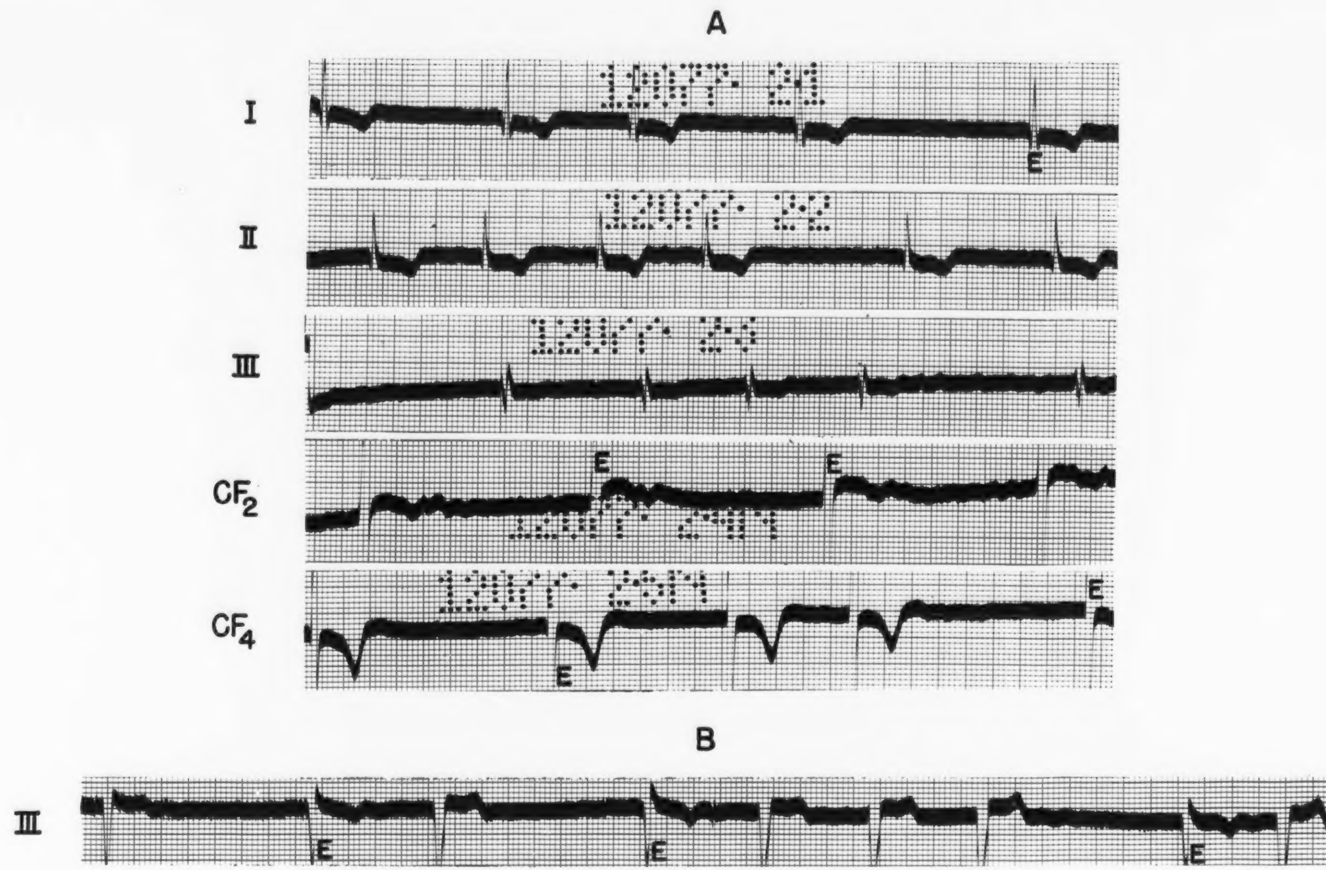

FIG. 2.—*A*, Electrocardiogram of Patient 8, showing a typical instance of auricular fibrillation with slow ventricular rate (average rate 45 per minute) and A-V nodal escapes (E) corresponding to a nodal rate of 34 per minute. *B*, Electrocardiogram of Patient 1, showing auricular fibrillation with slow ventricular rate (average rate 55 per minute) and A-V nodal escapes corresponding to a rate of 38 per minute. Note that the A-V nodal escapes (E) show aberrant conduction.

(The above two factors having an opposite effect upon the length of the first escape interval may operate simultaneously and balance each other.)

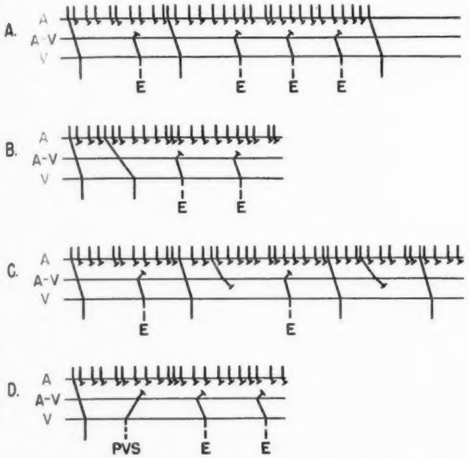

FIG. 1.—Diagrammatic representation of four instances of auricular fibrillation with A-V nodal escapes. *A*, Progressive shortening of the escape interval when several escapes occur in succession. (Compare fig. 3.) *B*, Delayed A-V conduction below the site of the nodal pacemaker shortens the first escape interval. *C*, Effect of "concealed conduction" in the A-V junction. Discharge of the A-V node by an impulse which is blocked below the nodal pacemaker may cause a delayed appearance of a nodal escape or its failure to appear. In the latter instance two conducted beats are separated by an R-R interval longer than the escape interval. *D*, Apparent lengthening of escape interval following a ventricular premature systole. (Compare fig. 4.)

In the diagrams (A) represents the auricular stimulation; (V) the ventricular stimulation (a solid line represents a ventricular beat conducted from the auricles, a broken line (E) denotes one initiated by the A-V node, and a dotted line (PVS) represents a premature ventricular systole); (A-V) represents the A-V nodal junction; and the oblique lines indicate conduction across this junction.

3. So-called concealed conduction of a supraventricular impulse in the A-V junction may influence the time of appearance of an escape. This has been demonstrated[3, 4] in patients with sinus rhythm and in those with auricular flutter. In these patients such impulses may penetrate into the A-V junction without traversing it; although they fail to reach the ventricles they may reach and discharge the secondary pacemakers in the A-V node. As a result of such discharge of the nodal pacemaker by a nonconducted impulse the "time table" of the secondary pacemaker is disturbed; thus, the appearance of an expected A-V nodal escape may be delayed. However, it may be entirely eliminated if, following the discharge of the nodal pacemaker by the blocked impulse, the A-V junction has recovered sufficiently to transmit an auricular impulse before a delayed escape takes place. Under such circumstances (fig. 1, *C*) one R-R interval would be appreciably longer than the escape intervals; the ventricular complex terminating the longest R-R interval would represent either a delayed A-V nodal escape or a conducted beat. Thus, under exceptional circumstances in a record with auricular fibrillation and nodal escapes the beat terminating the longest R-R interval may be a transmitted one, and the failure of the expected escape to appear may not invalidate the identification as nodal escapes of beats terminating a shorter R-R interval.

4. If an escape follows a ventricular premature systole (fig. 1, *D* and fig. 4) the escape interval may be longer than that of the escape following a conducted beat because of the tendency of the extrasystolic impulse to conduct retrogradely and to discharge the A-V nodal pacemaker. Figure 1, *D* shows that the lengthening of the escape interval after a ventricular premature systole is accounted for by the time for retrograde conduction from the extrasystolic focus to the site of the secondary pacemaker plus the time for forward conduction of the nodal escape.

5. Finally, slight variations of the escape intervals may be due to a slight arrhythmia of the secondary pacemaker as a result of varying vagal tone.

Summary and Conclusion

1. Based upon the experience with A-V nodal escapes in the presence of sinus rhythm an analysis was made of A-V nodal escapes occurring in the presence of auricular fibrillation.

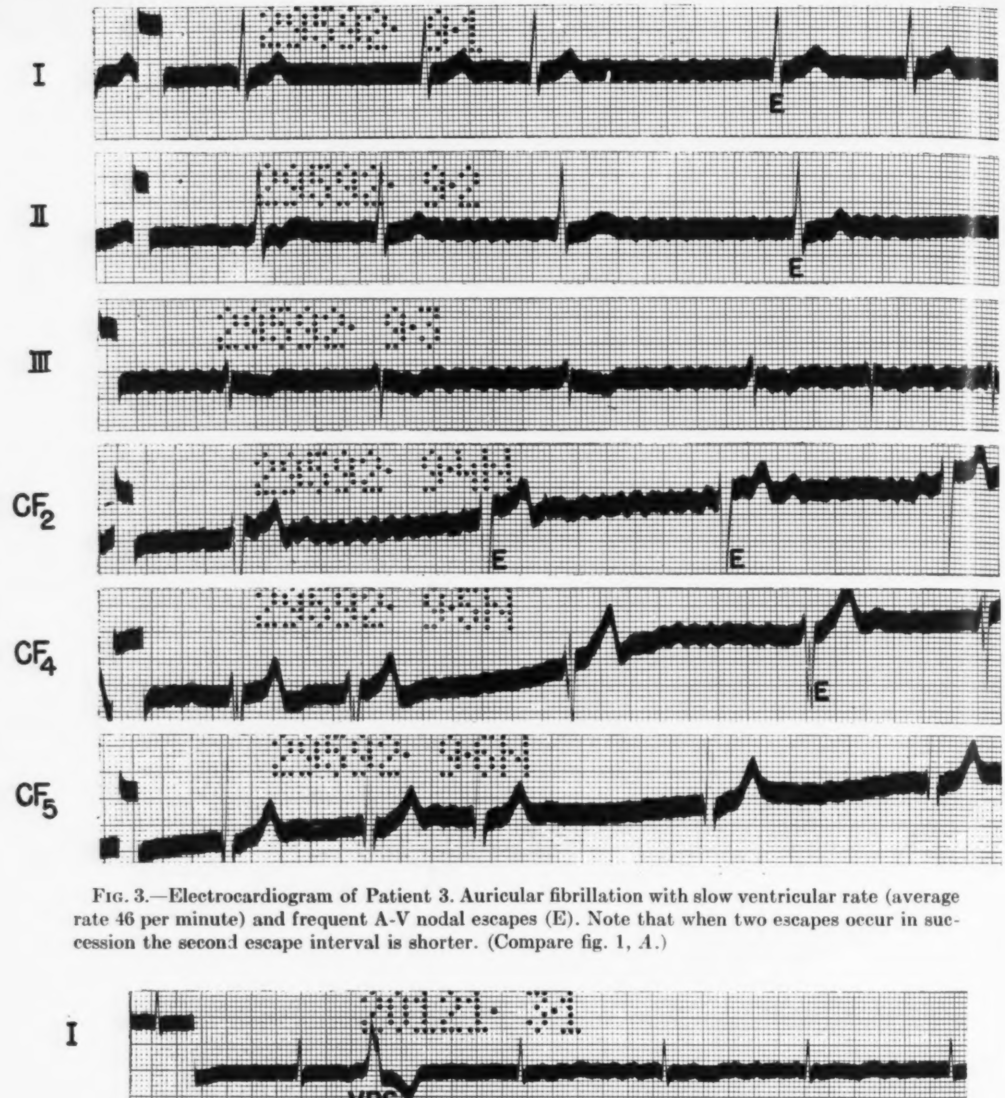

FIG. 3.—Electrocardiogram of Patient 3. Auricular fibrillation with slow ventricular rate (average rate 46 per minute) and frequent A-V nodal escapes (E). Note that when two escapes occur in succession the second escape interval is shorter. (Compare fig. 1, *A*.)

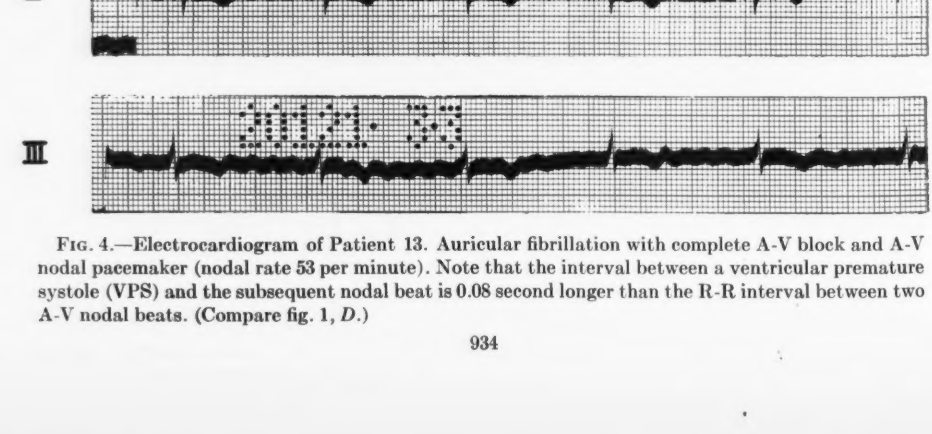

FIG. 4.—Electrocardiogram of Patient 13. Auricular fibrillation with complete A-V block and A-V nodal pacemaker (nodal rate 53 per minute). Note that the interval between a ventricular premature systole (VPS) and the subsequent nodal beat is 0.08 second longer than the R-R interval between two A-V nodal beats. (Compare fig. 1, *D*.)

The material consisted of a series of twenty-five records obtained on 16 patients with auricular fibrillation exhibiting marked ventricular slowing as a result of digitalis medication.

2. The criteria for the diagnosis of A-V nodal escape in the presence of auricular fibrillation are defined and the factors responsible for variations are discussed.

Acknowledgment

The authors are indebted to Dr. Louis N. Katz for his suggestions and criticisms.

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A Case of Paroxysmal Auricular Tachycardia with Block Present almost Continuously for Twenty-Five Years

By William B. Schwartz, M.D., and Samuel A. Levine, M.D.

The following case report is that of a man who showed electrocardiographic and clinical evidence of paroxysmal auricular tachycardia with block most of the time during a twenty-five year period of observation. The auricular rate was almost always in the vicinity of 200 per minute and the A-V ratio varied between 1 to 1 and 1 to 4. On only one brief occasion was there evidence of congestive failure. He was able to go through two major surgical operations without any difficulty and at present at the age of 79 years he is still ambulatory without cardiac symptoms.

The purpose of this paper is to present a case of paroxysmal auricular tachycardia with block which has persisted almost continuously for twenty-five years. Although cases have been reported in which paroxysms of auricular tachycardia with block occurred over long periods of time, there have been no reports of this arrhythmia continuing for many years.[1]

The differential diagnosis between paroxysmal auricular tachycardia with block and auricular flutter with A-V block frequently requires considerable care. In fact, they are considered by some to be of the same nature.[2] An important criterion for the electrocardiographic differentiation of the two disorders lies in the fact that the string is quiescent between successive auricular deflections in the case of paroxysmal auricular tachycardia with block, and is in continual motion in auricular flutter. In addition, the P waves are usually small and peaked in contrast to the slurred, triangular notched P waves found in auricular flutter. The concept has recently been proposed that paroxysmal auricular tachycardia with block is due to a circus movement in which the pathway goes through the A-V node.[3]

Case Report

J. M., P.B.B.H. No. S-80019. The patient is a 79 year old man who is now in a convalescent hospital with no symptoms referable to the cardiovascular system, and whose only complaints are weakness and mental depression. Physical examination shows no evidence of congestive heart failure. This patient was first seen in 1924 when he complained of precordial pain with radiation to the left arm. Physical examination revealed a regular heart rate of 120, blood pressure of 87/75, no pulmonary congestion, and a diastolic gallop rhythm. The white blood count was 6,400 and there was no elevation of temperature. The diagnosis made at this time was myocardial infarction. The electrocardiogram on admission revealed paroxysmal auricular tachycardia with 2:1 heart block (ventricular rate 120) and right bundle branch block. One week later the electrocardiogram showed paroxysmal auricular tachycardia with auricular and ventricular rates of 240 per minute. Shortly afterwards the apical rate fell to 120, but a second electrocardiogram revealed that the auricular rate was still 240 with 2:1 heart block. Later, on reviewing the data, it appeared that the symptoms were probably due to the tachycardia itself, and that the original diagnosis of myocardial infarction was incorrect. During the next twenty-five years the patient was seen, often several times a year, with complaints of palpitation and precordial and epigastric distress occurring in "spells" or "attacks" lasting several hours or days. It soon became clear that these "attacks" were associated with periods of rapid heart action which were demonstrated to be paroxysmal auricular tachycardia with a 1:1 response. In addition, on many occasions when the ventricular rate was slow and the patient had no symptoms, it was found that the auricles were beating at a rate of 200 or more per minute with 2:1, 3:1 or 4:1 heart block. The various changes in the cardiac mechanism are illustrated in figure 1. Electrocardiograms were taken on many occasions when the ventricular rate was slow, and in the majority of instances the auricles were found to be rapid. It is presumed that this also occurred at many other times when the ventricular rate was

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slow but no electrocardiograms were taken. The tracings always showed right bundle branch block.

Despite frequent attacks of tachycardia there was evidence of congestive failure on only one occasion. This occurred in 1928, four years after the arrhythmia was first diagnosed, and lasted for several days. In 1946, at the age of 76, the patient underwent two operations, including a perineal prostatectomy, with no ill effects. Repeated electrocardiograms both before and after the operation

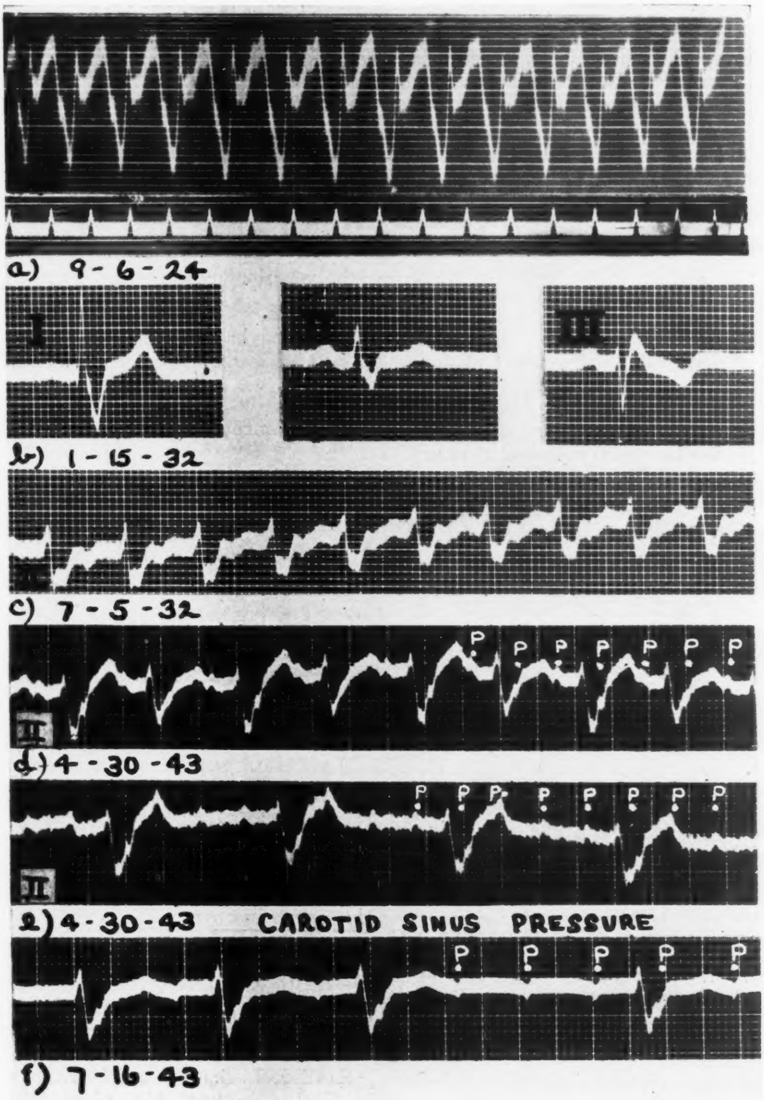

FIG. 1.—The various changes in the cardiac mechanism of the patient (J.M., a 79 year old man). (a) Auricular and ventricular rates 240. (b) Shows the rare occasion when normal sinus rhythm was present. Right bundle branch block is evident. (c) Rate 162. One to one rhythm. (d) Auricular rate 260, ventricular rate 130. (e) Carotid sinus pressure reveals the rapid auricular rate in "d" when 4:1 block was produced. (f) Irregular ventricular response (2:1, 4:1) with auricular rate 162. Note that P waves are inverted.

showed constant presence of auricular tachycardia with 2:1 block. During the twenty-five year period of observation the heart increased 2 cm. in transverse diameter as shown by x-ray examination.

Digitalization was carried out on several occasions without any evidence of beneficial effect on the incidence of recurring "attacks." On two occasions, adequate digitalis therapy slowed the ventricular rate by increasing the degree of block but without affecting the auricular tachycardia. It was frequently noted that it was possible to slow the ventricular rate by carotid sinus pressure. The reduction in rate was found to result from converting a 1:1 response to a 2:1 block or from a 2:1 to a 4:1 block. The auricular rate was not affected by this method of vagal stimulation. On six occasions, quinidine sulfate was effective in producing a normal sinus rhythm. Each time the rhythm reverted to normal on increasing amounts of quinidine, when a single dose of 0.5 or 0.6 grams orally was reached. The rhythm would not remain normal longer than some days or weeks despite the continued administration of 0.2 to 0.3 grams of quinidine three times daily. To our knowledge the first normal sinus rhythm occurred in 1928, following quinidine therapy, four years after the initial diagnosis of paroxysmal auricular tachycardia with block. At present the patient still has auricular tachycardia with block but no heart failure.*

Comments

There are several points of interest in this case. First, throughout most of these many years the auricles have been contracting at the rate of 200 per minute or over. This apparently has had no ill effect upon the circulatory efficiency or health of the patient. It was only when the ventricular response was very rapid and a 1:1 rhythm was present that symptoms resulted. Only on one occasion, lasting several days, was there objective evidence of congestive failure. Aside from this the patient remained ambulatory through most of the years of observation, and was able to undergo several major surgical procedures while auricular tachycardia was present.

Second, the possible benignity of right bundle branch block is indicated by the longevity of this patient. Attention has already been called to the fact that many cases of right bundle branch block do well and some are even associated with no other evidence of heart disease.[4] In this particular patient it is known to have been present constantly for at least twenty-five years.

In addition this case also demonstrates the similarity which may exist between the clinical features of acute myocardial infarction and paroxysmal rapid heart action. Here a mistaken diagnosis of the former was made on the first admission.

Medication was not of great importance in this case. However, digitalis in full doses slowed the ventricular rate when it was rapid without affecting the auricular tachycardia. Quinidine succeeded in restoring the rhythm to normal on six occasions, but the abnormal mechanism recurred in days or weeks even on so-called maintenance doses of quinidine.

* We are very grateful to Dr. John Mahoney, Resident Physician at the Holy Ghost Hospital, Cambridge, Mass., for information concerning the present status of the patient.

Summary

A case of paroxysmal auricular tachycardia with A-V block and right bundle branch block is described in which the auricular rate was over 200 per minute most of the time during a period of twenty-five years' observation. The patient was ambulatory practically all of this time, went through major surgical procedures satisfactorily and at present at the age of 79 years still shows no evidence of heart failure. The effects of digitalis and quinidine on the arrhythmia are discussed.

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Paroxysmal Tachycardia

Experiences with Massive Doses of Quinidine Intravenously in a Refractory Case

By George O. Bell, M.D., Robert B. Bradley, M.D., and Lewis M. Hurxthal, M.D.

An interesting case of recurrent paroxysmal tachycardia is presented. The patient had had a previous coronary thrombosis, leaving in its wake a residual left bundle branch block. Three episodes of paroxysmal tachycardia were observed, the longest one of sixty-three days' duration. Although ventricular origin of the tachycardia was thought to be most likely, a nodal origin was also considered. All forms of therapy were tried but only intravenous quinidine proved to be successful. Experiences with massive doses of quinidine intravenously are presented.

PAROXYSMAL tachycardia occurring in patients with organically sound hearts is always a burden and especially so if it is prolonged. When such an abnormally rapid heart rate occurs in patients who have previous myocardial damage the threat to life is indeed real. The conversion of the tachycardia to normal sinus rhythm must be accomplished as quickly as possible to avoid a fatal outcome. The case herein reported proved to be extremely refractory to all treatment and only after heroic measures were used was success attained.

Although the exact nature of the tachycardia in the present case remains uncertain, the therapeutic procedures used may be of some interest to others who are confronted with the problem of treating patients with stubborn cases of paroxysmal rapid heart action.

Case Report

R. T., a 44 year old white, married clerk, was first seen at the Lahey Clinic on October 22, 1946, complaining of rapid heart action of eighteen days' duration. His past history revealed the occurrence of a coronary occlusion in December 1941. Electrocardiographic changes were characteristic of an anterior myocardial infarction. Recovery from the episode was prompt and he was able to return to his usual work three months later. Following the attack of 1941 until October 1946, six episodes of paroxysmal rapid heart action had occurred, each lasting about twelve hours and responding to simple measures such as administration of digitalis, morphine, or sodium pentobarbital and a night's sleep. On October 4, 1946, he suffered a sudden attack which failed to respond to the usual measures.

On examination, on October 22, the heart was found to be beating rapidly (180) and regularly but with some slight unevenness of the apical sounds. Vagal stimulation by pressure on both carotid sinuses produced no slowing. Electrocardiograms showed a tachycardia with QRS interval of 0.12 second (fig. 1, A).

The administration of 20 mg. Mecholyl subcutaneously produced flushing and substernal distress, but no change in the heart rate.

The next day 0.6 Gm. quinidine sulfate given intravenously over a period of fifteen minutes slowed the apex rate from 180 to 140. The same dose was repeated and slowed the apex rate to 130. Four hours later 2 cc. (1.0 mg.) Prostigmine methyl sulfate administered intramuscularly produced no change in the abnormal rhythm.

During the next four days (October 24–27, 1946, inclusive) the patient remained in bed at home and was given quinidine sulfate orally, 0.4 Gm. every three hours. At times his apical rate slowed to 90 beats per minute.

First Hospital Admission. On October 28, 1946, the patient was hospitalized for further treatment. An electrocardiogram verified the presence of the abnormal rhythm with a ventricular rate of 160. He was given 1.5 mg. Prostigmine, followed in five minutes by 5 mg. Mecholyl administered subcutaneously. This combination of drugs produced vigorous vagal stimulation characterized by profuse sweating, rhinorrhea, lacrimation, nausea, vomiting, severe abdominal cramps, diarrhea and micturition, but no change whatever in the tachycardia. Atropine sulfate (1.2 mg. given intravenously) terminated this reaction.

The following day, October 29, 1946, 20 cc. of a 25 per cent solution of magnesium sulfate given intravenously had no effect on the tachycardia.

During the next three days treatment consisted of a daily ration of quinidine sulfate (1.0 Gm.)

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and potassium chloride (10 Gm.) given by mouth. Because of marked discouragement on the part of the patient he was discharged on November 2 to admitted to the hospital with congestive heart failure. He was critically ill, with an apical heart rate of 172, cardiac enlargement, basal pulmonary

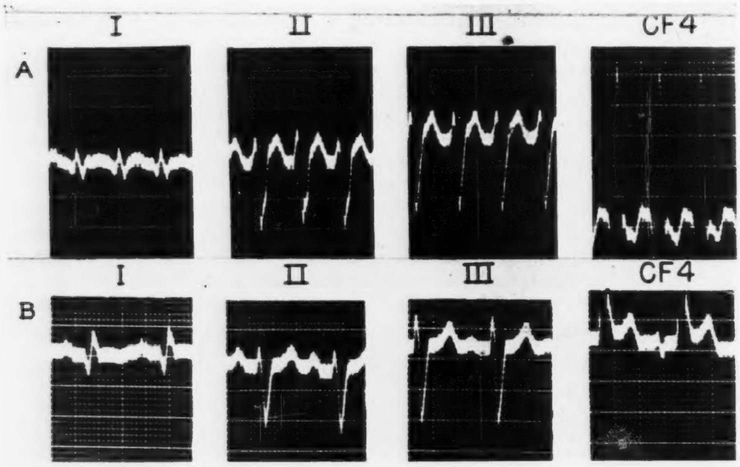

FIG. 1.—*A*, October 22, 1946. Paroxysmal tachycardia. Rate 208. *B*, November 10, 1946. One day following conversion to sinus rhythm. Rate 110. P-R, 0.20 second. Delayed intraventricular conduction, QRS, 0.13 second. T_1 inverted.

FIG. 2.—December 1946. Left ventricular enlargement. Cardiothoracic ratio, 15.2 to 30.5 centimeters.

continue the same dosage of quinidine and potassium chloride at home.

Second Hospital Admission. On November 9, 1946, one week after discharge, the patient was re-

râles, enlarged tender liver, and distention of the veins of the neck.

Quinidine hydrochloride* (1.8 Gm. in 300 cc. of 5 per cent glucose solution) was administered intravenously over a period of one and one-half hours. The heart rate slowed from 172 to 120 beats per minute. Potassium acetate (0.5 Gm.) was then given every two hours, and after the third dose the heart rate dropped to 88. The electrocardiograms (fig. 1, *B*) showed a normal sinus rhythm with a rate of 110, P-R interval of 0.2 second, QRS complex 0.13 second in duration, and inverted T wave in Lead I. Total duration of this attack of tachycardia was thirty-seven days.

During the remainder of this hospital stay the patient was maintained on 0.8 Gm. quinidine sulfate and 4 Gm. potassium acetate per day. The congestive heart failure responded to low-salt diet and diuretics. Digitalis was avoided because of the possible danger of reinstigating the abnormal tachycardia. The patient was discharged on November 26, on a program of markedly restricted activity, 0.2 Gm. quinidine sulfate three times daily, and 0.033 Gm. phenobarbital three times daily.

The patient was seen at varying intervals during the next four months. In December 1946 a roentgenogram of the chest showed clear lung fields and left ventricular enlargement (fig. 2). He maintained a normal sinus rhythm with an average apex rate of 90 to 100. Because of easy dyspnea, digitoxin

* Brewer and Company, Inc.

therapy was started and maintained for the next three months. The patient returned to work in January 1947 and remained fairly well, except for mild angina on effort.

Third Hospital Admission. On March 10, 1947, the patient was admitted to the hospital for the third time because of rapid heart action which had started suddenly the day before without obvious precipitating cause. The apex rate was approximately 200 beats per minute, with slight irregularity of rhythm and slight variation in intensity of heart sounds. The electrocardiograms showed a ventricular rate of 204 with QRS interval of 0.17 second duration (fig. 3, *A*). The patient's general condition was good and there were no signs of cardiac decompensation.

Vagal stimulation by means of eyeball pressure, carotid sinus pressure, gagging, and the Valsalva maneuver were without effect. Heavy dosage of morphine given subcutaneously provided the patient with a good night's sleep but was without influence on his tachycardia.

The next day he was given 180 mg. procaine (18 cc. of 1 per cent solution) intravenously within four minutes. Sodium pentothal was given concomitantly to control the toxic effects on the central nervous system. There was no change in cardiac rhythm although the rate fell from 200 to 156 per minute.

Several hours later the patient was given 0.2 Gm. quinidine orally, and potassium chloride (4 Gm. initially and 2 Gm. every two hours) and quinidine hydrochloride (1.8 Gm. in 200 cc. of 5 per cent glucose solution) intravenously over a period of one and one-half hours. The apex rate fell from 206 to 88 at which point the mechanism reverted to a normal sinus rhythm. Total duration of this paroxysm was two days. The patient was maintained on oral quinidine sulfate (0.2 Gm. four times a day) and potassium acetate (1.0 Gm. four times a day). Electrocardiograms made following conversion to normal rhythm showed a rate of 72 with a P-R interval of 0.28 second and QRS wave of 0.17 second's duration and left bundle branch block (fig. 3, *B*). He was discharged on March 15.

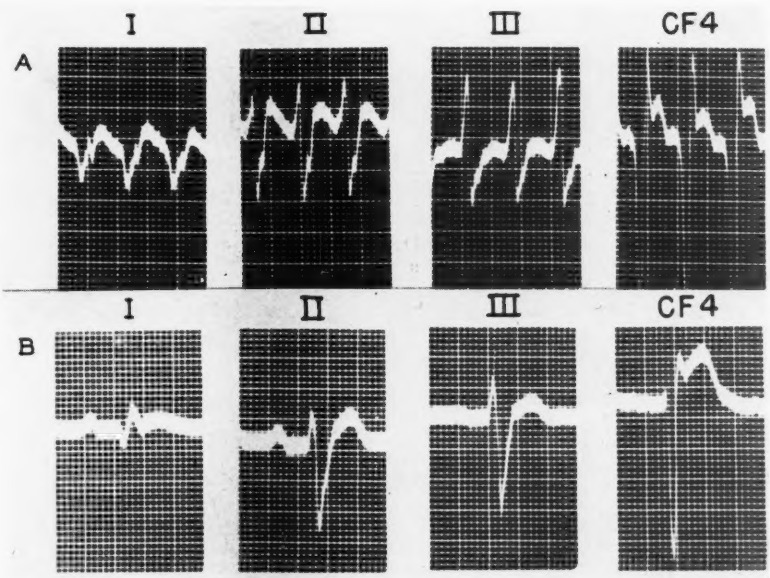

FIG. 3.—*A*, March 10, 1947. Paroxysmal tachycardia. Rate 204. *B*, March 11, 1947. Following intravenous quinidine therapy. Normal sinus rhythm. Rate 72, delayed A-V and I-V conduction, P-R, 0.28 second. QRS, 0.17 second.

From March 1947 to September 1948 (seventeen months) the patient worked steadily at his usual job with no complaints other than anginal pain on unusual exertion. In February 1948 his electrocardiogram showed a rate of 110, P-R interval of 0.20 second, QRS wave of 0.16 second's duration, and a left bundle branch block. He continued taking 0.2 Gm. quinidine sulfate four times daily and 1 Gm. potassium acetate twice daily, and on this program he remained free of further episodes of tachycardia.

Fourth Hospital Admission. On September 2, 1948, he was admitted to the hospital again for treatment of rapid heart action which began that morning shortly after he was informed of a promo-

tion in his work. Physical examination showed no abnormality except for slight cardiac enlargement and an apical rate of 160 per minute. Slight variation in intensity of heart sounds and irregularity in the rhythm were again noted. Signs of congestive failure were absent.

During the first four days quinidine was given orally in doses of from 2.4 to 4.8 Gm. per day along with 24 Gm. potassium acetate per day. Morphine sulfate was given at various times, usually 15 mg. subcutaneously and occasionally intravenously. The abnormal rhythm persisted although the apical rate was slowed from 160 to 110–120.

ventricular tachycardia occurring in the presence of a left bundle branch block. In view of this cardiogram and also since the quinidine therapy had failed, it was decided to give digitalis a trial. Cedilanid administered intravenously in a dosage of 1.6 mg. had no influence on the electrocardiogram nor on the clinical findings.

On September 9, intravenous administration of quinidine (1.8 Gm.) again failed to establish a normal rhythm.

After these two failures of intravenous quinidine therapy it was decided to administer digitoxin to its fullest effect. Digitoxin was given orally in a dose

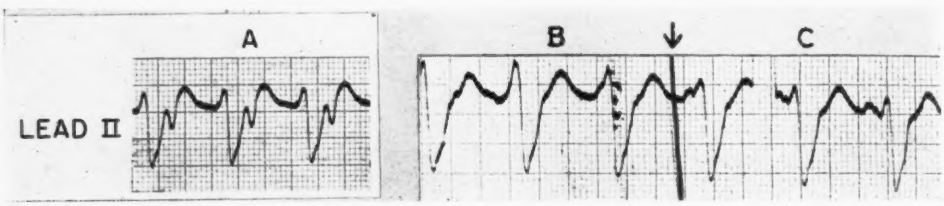

FIG. 4.—September 7, 1948. Lead II only. (*A*), Paroxysmal tachycardia, (*B*), during intravenous quinidine therapy showing (*C*), conversion to sinus rhythm.

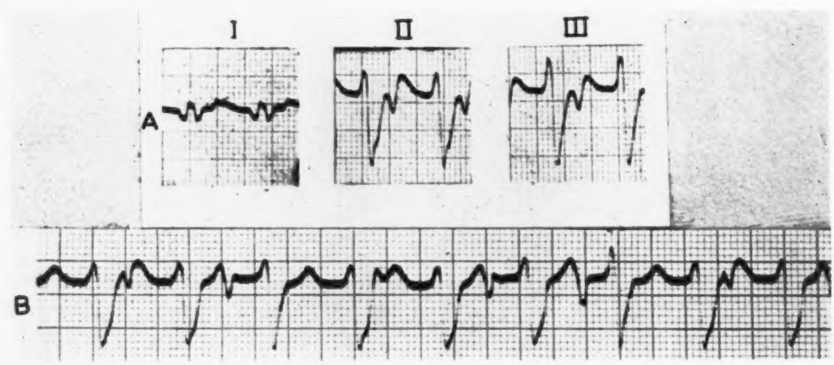

FIG. 5.—*A*, September 8, 1948. Paroxysmal tachycardia with a P wave following each ventricular complex. *B*, October 16, 1948. Retrograde P waves, in ratio of three P waves to four QRS complexes.

On September 7, 1948, quinidine was given intravenously in a dose of 1.8 Gm. in 300 cc. of 5 per cent dextrose in saline solution. Potassium chloride was administered throughout the period of treatment in 2-Gm. oral doses every two hours. Normal sinus rhythm (fig. 4) was established after 1.2 Gm. quinidine had been administered. One hour after the cessation of intravenous quinidine therapy, however, tachycardia reappeared, despite continued oral administration of quinidine and potassium, given to the point of nausea.

The next day, September 8, the electrocardiogram showed a perfectly regular although abnormal rhythm (fig. 5, *A*) which suggested a supra-

of 0.2 mg. every eight hours for the next two days, September 11 and 12. On the second day of this program the apical rate steadily increased from the average basal rate of 120 up to 180 per minute. With this manifestation of digitalis toxicity it was apparent that further pursuance of this program would not only be unsuccessful but would also be dangerous. Digitoxin therapy was therefore abandoned and the oral administration of quinidine was resumed in a dosage of 0.4 Gm. every four hours. The ventricular rate was maintained between 120 and 140 per minute on this program.

On September 14, prostigmine methyl sulfate (1.0 mg. given intramuscularly) and prolonged pres-

sure first on both eyeballs and then on both carotid sinuses had no effect.

On September 15, acetylcholine was administered intravenously rapidly (within one second) in doses of 35 mg., then 60 mg., and finally 100 mg. with no effect on the tachycardia.

On September 17, the intravenous quinidine program was repeated. Potassium chloride was given in dosage of 2 Gm. every hour for four doses. A total of 1.8 Gm. quinidine over a period of one hour and fifty-five minutes failed to convert the tachycardia to normal sinus rhythm. At the completion of the quinidine injection, atropine sulfate (1.2 mg. given intravenously) had no effect.

On September 18, 0.1 Gm. Papaverine given intravenously produced a marked generalized flush but no change in cardiac rate or rhythm. A roentgenogram of the chest showed the same findings as previously noted, but for the first time calcification was noted in the pericardium of the left ventricle (fig. 6).

On September 25, a fourth trial of intravenous quinidine was given as before. Three grams of potassium chloride were given in a single dose ninety minutes after beginning the quinidine. The patient received 1.8 Gm. quinidine in one hundred and sixty-five minutes. Normal sinus rhythm appeared one hundred and twenty-five minutes after the start of quinidine and thirty-five minutes after the dose of potassium chloride. Maintenance therapy consisted of 0.4 Gm. quinidine sulfate and 1.0 Gm. potassium chloride every four hours. Normal sinus rhythm remained for a period of twelve hours at which time the patient vomited, the ventricular rate increased to 115 beats per minute, and the abnormal rhythm reappeared.

On September 28, three days later, the fifth trial of intravenous quinidine was given in the same manner. This attempt was unsuccessful in spite of reduction of the ventricular rate to a low of 84 per minute.

On October 2, thirty days after the onset of his tachycardia, a bilateral procaine block of the inferior cervical ganglions plus the first four thoracic sympathetic ganglions was performed.* Good physiologic effect was obtained, as manifested by bilateral Horner's syndrome, increased warmth of the arms and hands, and absence of sweating on face and arms. Vagal stimulation was also done by means of eyeball and carotid sinus pressure. There was no change demonstrable either clinically or by electrocardiogram.

On October 6, four days later, the bilateral procaine block was repeated. This time the patient was given 0.6 Gm. quinidine orally every four hours for forty-eight hours prior to the block. Again, there was no effect on the tachycardia. Atropine sulfate (2.0 mg.) given intravenously did not change the abnormal rhythm. Four hours later Prostigmine (1.5 mg. given intramuscularly) was likewise unsuccessful.

On October 7, the intravenous quinidine regimen was applied for the sixth time. The electrocardiogram showed the appearance of normal sinus rhythm after 1.0 Gm. had been administered. Sinus rhythm alternated with the tachycardia repeatedly during the next one hundred and ten minutes, during which time an additional 0.8 Gm. quinidine was given.

FIG. 6.—September 18, 1948. Calcification in pericardium over left ventricle.

Forty-five minutes after the discontinuance of the quinidine injection the electrocardiogram showed that the abnormal tachycardia had persisted. That night the patient retained 2.0 Gm. potassium given orally every two hours, except for two doses, and 0.6 Gm. quinidine given every four hours. An electrocardiogram taken the next morning (fig. 7) suggested the possibility of potassium intoxication although the patient showed no clinical signs of this condition.

From October 8 to October 13 the patient was maintained on quinidine sulfate (0.2 Gm. every four hours). The ventricular rate averaged about 140 per minute or less. During this time, diarrhea from medication increased to eight or ten stools per day, and anorexia was moderately severe.

* Suggested by Dr. Samuel A. Levine.

On October 13 the patient received 20 cc. of a 25 per cent solution of magnesium sulfate intravenously in a period of two minutes. This produced severe flushing and sweating, but had no effect on his heart except for slight slowing of the ventricular rate (140 to 120 per minute).

On October 15 the same quinidine regimen as that used on October 7 was tried. Conversion to a sinus rhythm occurred after slightly less than 1.0 Gm. had been given. On this occasion, the abnormal rhythm reappeared between one and two hours after the treatment had been terminated.

On October 16 the patient developed pleuritic pain in the lower portion of the right side of his chest. A roentgenogram of the chest showed a high diaphragm on the right side, mottled density throughout the base of the right lung, and slight shift of the mediastinum to the right; these findings were interpreted as evidence of atelectasis and a superimposed pneumonitis. Fever, chest pain, and râles at the right base responded slowly to penicillin therapy. On October 25 the roentgenograms showed an increase in the density at the base of the right lung; this was interpreted as evidence of pneumonia, pleuritis, and fluid, although the possibility of a pulmonary infarct could not be entirely excluded.

On October 30 the patient showed evidence of congestive heart failure. Mercurial diuretics, xanthines, and acid-ash, salt-free (1.5 Gm. salt or less) diet were effective in relieving the symptoms to some extent. During this interim the tachycardia continued without change. The patient's daily quinidine ration kept the rate at an average level of 120 to 130.

It became evident that the patient was showing increasing dependence on morphine. His daily intake of morphine had been limited to 15 mg. at bedtime with occasionally an extra dose during the day. Attempts at withdrawal were accompanied by mental depression, anxiety, apprehension, paranoid tendencies, and increase in diarrhea.

On November 3 the intravenous quinidine regimen was attempted for the eighth and final time. Since the previous successful conversions to normal rhythm had failed to establish the sinus rhythm for more than twelve hours, the plan adopted on this trial was to give quinidine until normal sinus rhythm appeared and then to maintain this rhythm by constant slow intravenous drip of quinidine over a period of several hours. In this way, we hoped to depress the irritability of the ectopic focus long enough to permit the sinus node to recapture its dominance.

Quinidine hydrochloride, 1.8 Gm. in 300 cc. of normal saline solution, was given intravenously. Sixty-five minutes after starting the quinidine and twenty minutes after the oral administration of 2.0 Gm. potassium chloride, the electrocardiogram showed a normal sinus rhythm with a ventricular rate of 106 per minute.

The initial 1.8 Gm. quinidine was administered in a period of two hours, after which an additional 1.8 Gm. was started. At this time the apex rate was 88 per minute. The flow of quinidine solution was reduced to a rate of 5 to 8 drops a minute.

Four hours later an electrocardiogram (fig. 8) showed normal sinus rhythm with a rate of 70. The patient at that time responded poorly to commands and his breathing became irregular. The flow of quinidine solution was stopped, a total dose of 3.2 Gm. having been administered. Five minutes later he was completely unresponsive, his breathing ceased, and his heart sounds could not be heard. An electrocardiogram (fig. 8) showed loss of P waves and marked widening of the QRS complex. Neo-synephrine (3 mg.) was given intravenously and the heart sounds became audible with an apical rate of 96. An additional 10 mg. Neosynephrine and 0.5 Gm. caffeine were administered intravenously followed by a marked improvement in the heart sounds.

The patient was placed in an oxygen tent and within an hour he regained full consciousness, cyanosis decreased, normal sinus rhythm remained with an apex rate of 90 to 100, but the blood pressure was still unobtainable.

During the ensuing twenty-four hours the blood pressure gradually rose to 80/60. The sinus rhythm persisted. Anuria occurred and the patient complained of marked thirst. Edema appeared in the feet and ankles. The nonprotein nitrogen rose to 78 mg. per 100 cc. of blood, the serum carbon-dioxide combining power was 25 volumes per cent, and the serum chloride was 446 mg. per 100 cc. of serum.

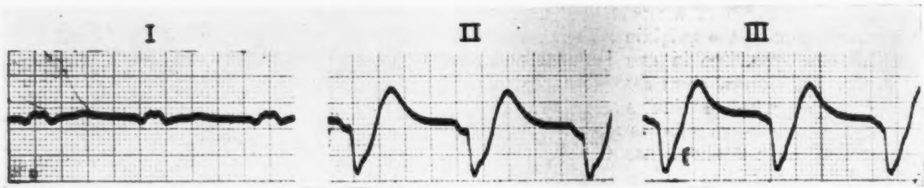

Fig. 7.—October 8, 1948, one day following intravenous quinidine (1.8 Gm. total) and maintenance oral quinidine (0.6 Gm. every four hours) along with potassium acetate (2.0 Gm. every two hours). QRS, 0.20 second. Absence of P waves and widened QRS waves are suggestive of potassium poisoning.

The patient was given fluids freely by mouth, 350 cc. of human plasma intravenously, and additional caffeine and Neosynephrine intramuscularly. On November 4 a total of 55 cc. of urine was obtained by catheterization during the twenty-four hours. On November 5 urinary output returned to normal levels. The duration of the urinary suppression was forty-two hours.

From this point on the patient began to improve slowly and steadily. The serum nonprotein nitrogen, chloride, and carbon-dioxide combining power returned quickly to normal levels. Edema decreased and the blood pressure rose to around 100/60–70. The final electrocardiogram (fig. 9) showed a normal sinus rhythm. The addiction to morphine was the only problem of significance and it was gradually corrected after withdrawal of the drug. The patient was discharged from the hospital on November 16, seventy-five days after admission. The duration of his paroxysmal tachycardia was sixty-three days.

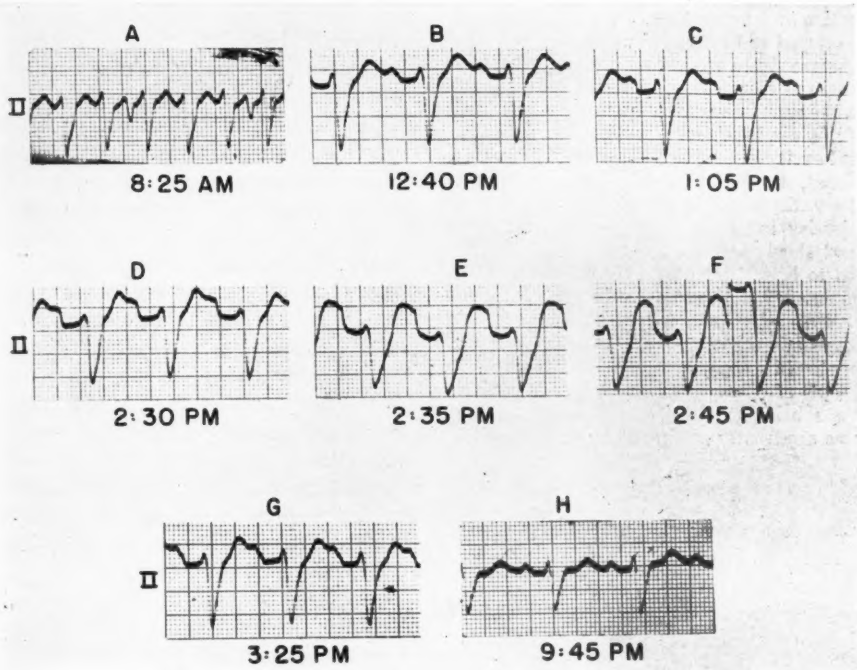

FIG. 8.—November 3, 1948. Lead II only. During intravenous quinidine therapy (3.2 Gm. total). *A*, Paroxysmal tachycardia, *B*, sinus rhythm, *C*, *D*, *E*, *F*, progressive changes showing quinidine toxicity. *G*, recovery from toxicity. *H*, eight and one-half hours later, normal sinus rhythm.

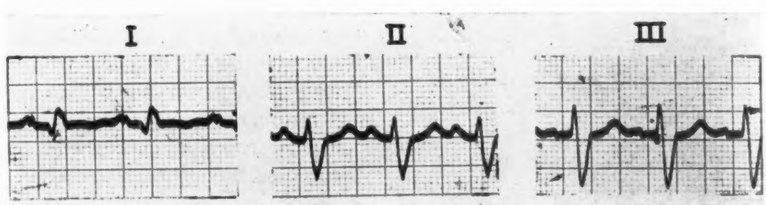

FIG. 9.—November 15, 1948. Normal sinus rhythm. Rate 92. P-R, 0.18 second. Delayed intraventricular conduction. QRS, 0.13 second. (The most recent electrocardiogram, January 10, 1949, showed normal sinus rhythm. Rate 110. Delayed A-V conduction. P-R, 0.22 second. Left bundle branch block. QRS 0.16 second in duration.)

Following his discharge from the hospital the patient was maintained on 1.0 Gm. quinidine sulfate daily and an occasional injection of Mercuhydrin.

Activity was gradually increased and well tolerated until he contracted an acute upper respiratory infection in January 1949. A severe paroxysmal cough developed and interfered with sleep. Dyspnea became progressively worse and because of this he was readmitted to the hospital where he remained for fifteen days. Because of hydrothorax on the right side, secondary to congestive heart failure, the pleural cavity was tapped twice and 1,850 cc. of straw-colored, transudative fluid were removed. While the patient was in the hospital acute and severe pleurisy involving the lower left side appeared and slowly cleared up. Although this was considered to be inflammatory, the possibility of a small pulmonary infarct could not be excluded.

The patient was discharged on February 3 and seen at the clinic on February 17, 1949. His heart had maintained its normal sinus rhythm, and there were no signs of congestive heart failure. Physical activity was being resumed very slowly and the patient was apparently getting along satisfactorily.

Discussion

The diagnosis of this patient's tachycardia has been in doubt. We do know that the patient has a left bundle branch block and the tachycardia has been engrafted upon this. Retrograde conduction of the impulse from ventricles to auricles seems to be definite and inverted P waves are found to occur at varying intervals following the QRS complexes. In figure 5, *A* an inverted P wave follows each QRS complex. In figure 5, *B* an inverted P wave follows the QRS wave at progressively increasing intervals—the "reverse Wenckebach" with a 4:3 and 3:2 retrograde block. Regularly occurring P waves independent of the ventricular rhythm have not been identified. In the absence of this proof, ventricular tachycardia cannot be diagnosed with certainty in spite of the fact that in many ways the tachycardia behaved very much like a ventricular tachycardia. The possibility that the ectopic focus was located somewhere in the junctional tissue must be entertained. The configuration of the QRS wave when sinus rhythm was restored is quite similar to the QRS wave noted during the tachycardia and this fact favors a supraventricular origin of the tachycardia. Whatever is the mechanism of the abnormal rhythm, the results of various forms of treatment are quite interesting.

Treatment of this patient's tachycardia included practically every form of therapy that has been recommended for such disorders of rhythm. Most forms of therapy were used more than once and in sufficiently high dosage to guarantee their full pharmacologic effect with the possible exception of intravenous morphine, in which our dosage was much below that recommended by Gonzales Sabathie.[4]

Methods of increasing vagal tone were totally ineffective. The administration of Prostigmine, Mecholyl, and acetylcholine, and the application of carotid sinus pressure were ineffective. The administration of Prostigmine followed within five minutes by Mecholyl produced such an array of symptoms that there was little doubt that vagal stimulation of marked degree was obtained and yet there was no significant alteration in the tachycardia.

Blocking the vagus by the intravenous administration of 2.0 mg. atropine after the patient had received heavy doses of quinidine[5, 12] orally likewise had no effect.

Blocking the sympathetic nervous pathways by the injection of procaine solution into the inferior cervical and first four thoracic ganglions on both right and left sides[1] was without effect. Several days before the first procaine block, oral quinidine therapy had purposely been discontinued to allow the ventricular rate to return to its maximum level. It was reasoned that the higher initial ventricular rate might serve as a better control for any change resulting from the procaine block.

Continuous electrocardiographic tracings and constant auscultation over the heart during the procedure disclosed no alteration in the abnormal cardiac rhythm. Carotid sinus pressure after this block produced no change.

The second sympathetic block was performed at a time when the patient was under the influence of high quinidine dosage. Again there was no noticeable effect on the rhythm and this time the intravenous administration of atropine was ineffective. Finally, the administration of prostigmine resulted in no change. These procedures demonstrated to us that blocking all cardio-accelerator impulses

while at the same time blocking the vagus chemically, and later stimulating the vagus chemically produced no change in the abnormal rhythm.

The use of a potassium salt in conjunction with quinidine[9, 11] during the first episode of tachycardia led us to believe that it was of definite value in terminating the abnormal rhythm. We suspect, however, as a result of the numerous failures during the last bout of tachycardia, that potassium salts played a questionable role in the successful conversion to normal rhythm.

Magnesium sulfate[2] was administered intravenously on two separate occasions and although there was severe flushing and sweating and some slowing of the ventricular rate, the basic rhythm remained unchanged. The dosage was adequate (20 cc. of 25 per cent solution) and the speed of injection was rapid (two minutes).

We do not wish to imply that all the abovementioned forms of therapy may be ineffective in other cases of paroxysmal tachycardia. They simply did not work in our patient.

The experience with digitalis in this patient was the same as noted by others.[3, 8] There was no beneficial effect on the tachycardia from the standard 1.6 mg. lanatosid C and as digitoxin was further administered there was a steady rise in the ventricular rate. It was apparent that further administration of digitalis was definitely hazardous.

Intravenous procaine administration had no effect on the tachycardia except to produce some slowing of the ventricular rate.

The only drug of any value in our patient was quinidine. Quinidine was given orally to the point of tolerance (4.8 Gm. a day). It was effective in slowing the ventricular rate from 170 or 180 to 110 or 120. Anorexia, nausea, occasional vomiting, and excessive diarrhea interfered with attempts to increase the dose by mouth. Slowing the ventricular rate even by that amount was of considerable value in delaying the onset of congestive heart failure. However, conversion to normal rhythm by oral administration of quinidine was not accomplished.

Quinidine hydrochloride given intravenously has been the only successful form of therapy in this patient. The first two attacks of paroxysmal tachycardia were terminated after a dosage of 1.8 grams. During the last episode, quinidine was administered intravenously on eight separate occasions. Four of these trials were total failures and four were marked by conversion to normal rhythm for variable periods of time. Previous administration of digitalis could possibly account for lack of success in at least two trials. A third trial with the intravenous quinidine failed to terminate the tachycardia in spite of slowing the ventricular rate to 84. The administration of more quinidine at this point seemed unwise. The fourth failure to convert was marked by a long period of alternating paroxysmal tachycardia and normal sinus rhythm. Perhaps in this instance a larger dose of quinidine might have been successful.

Of the times when intravenous quinidine therapy was at least temporarily successful, there were two occasions when the abnormal rhythm was converted to normal sinus rhythm after the administration of only 1.0 Gm. of the drug. In each case, however, an additional 0.8 Gm. was injected, with the intention of depressing the irritable focus long enough to permit full recovery of the sinus node. Normal sinus rhythm persisted for one hour and for two hours respectively. The third partly successful result was obtained with 1.8 Gm. quinidine. In this instance, maintenance oral quinidine was given in a dosage of 0.4 Gm. every four hours. Normal sinus rhythm remained for twelve hours, after which the paroxysmal tachycardia reappeared. A higher maintenance dose of quinidine may have prevented the return of the tachycardia. The fourth and last intravenous injection of quinidine terminated the tachycardia and established a normal sinus rhythm which has persisted to date. On that occasion the patient received 3.2 Gm. of the drug over a period of four hours. At the end of that time he developed clinical signs of toxicity[5] which included a state of coma during which he was completely unresponsive for a period of one hour, and had marked irregular respirations, cyanosis, and extreme weakness. The cardiac manifestations of toxicity included

pulselessness for a short period of time; cardiac sounds were not audible and the only way it was possible to ascertain whether or not he was still alive was by means of the electrocardiogram. His blood pressure fell until it was unobtainable, and only gradually returned to its usual level during the following twenty-four hours. Urinary suppression lasted forty-two hours and although this may be a manifestation of quinidine toxicity alone, it is more likely that the low blood pressure and a disturbed electrolyte balance were largely responsible.

The electrocardiogram (fig. 8) revealed a progressive loss of the P wave, widening of the QRS complex to 0.28 second, and an increase of the Q-T interval to 0.5 second. The Q-T interval had been lengthened by about 39 per cent which is much beyond the 25 per cent range of safety usually recommended.[6, 7, 10] This risk was deliberately taken since in this patient we found that the average intravenous dose of quinidine (1.8 Gm.), although successful on some occasions, failed completely on other trials. It, therefore, appears to us that the intravenous dosage of quinidine may vary not only from patient to patient, but also may vary in the same patient from time to time. It furthermore appears that when quinidine is used intravenously for the treatment of paroxysmal tachycardia it should be given in a dosage that is *large* enough to terminate the tachycardia. This may range from 0.6 Gm. to 1.8 Gm. or higher. If early recurrence of the tachycardia within the first twenty-four hours cannot be prevented by oral maintenance doses of quinidine, then the use of quinidine intravenously should be considered.

The final point of interest is the development of pericardial calcification over the left ventricle. It is quite possible that the area of calcification may involve the myocardium as well. Presumably this represents calcification following the original myocardial infarction. In time this may possibly further embarrass the heart. Whether or not it is playing a part in the recurrent tachycardia it is not possible to say.

Conclusions

A case of recurrent paroxysmal tachycardia is reported. Three separate attacks have been observed, one of thirty-seven days', another of two days', and a third of sixty-three days' duration.

Intravenous administration of quinidine was successful in terminating each attack. The dosage used was 1.8 Gm. quinidine hydrochloride in two attacks and 3.2 Gm. in the third.

Methods aimed at altering the nervous control of the cardiac rhythm were ineffective. Intravenous administration of magnesium sulfate and of procaine were also of no value. Digitalis failed to terminate the tachycardia and actually increased the heart rate.

The diagnosis of the type of tachycardia is uncertain although we consider it either a paroxysmal nodal or paroxysmal ventricular tachycardia in the presence of a left bundle branch block.

Calcification in the pericardium made its appearance during the two-year period of observation and the question was raised as to its possible role in the recurrent episodes of tachycardia.

Acknowledgment

We are indebted to Dr. Samuel A. Levine for his helpful suggestions and constructive criticism in the preparation of this paper.

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Relation of Supraventricular Paroxysmal Tachycardia to Heart Disease and the Basal Metabolism Rate

By R. W. Kissane, M.D., Richard Brooks, M.D., and Thomas E. Clark, M.D.

The records of 9,950 private patients were reviewed to determine the incidence of supraventricular paroxysmal tachycardia. The relationship of the tachycardia to the various types of heart disease was determined. The incidence of tachycardia in normal persons and in patients with hyperthyroidism or hypothyroidism was also studied.

SUPRAVENTRICULAR paroxysmal tachycardia has been described as occurring frequently in association with thyrotoxicosis and also with rheumatic heart disease; however, White[1] reported that 89 among a total of 132 collected cases occurred in persons who showed no evidence of heart disease. Fatigue was given so frequently as the responsible factor in precipitating the attack that it was suggested that a hypothyroid state should be studied for demonstration of any possible relationship between it and the tachycardia. In order to evaluate these impressions the following investigation was undertaken, using various types of standard commercial basal metabolism apparatus, under carefully controlled basal conditions.

Method and Results

A review of the records of 9,950 private patients from a cardiologic service revealed 361 cases of supraventricular paroxysmal tachycardia, or an incidence of 3.6 per cent. The cases of tachycardia were distributed as follows: 122, or 34 per cent, occurred in persons considered to be normal; 123, or 34 per cent, in patients with rheumatic heart disease; 51, or 14 per cent, in patients with arteriosclerotic heart disease; 12, or 3 per cent, in patients with hypertensive heart disease; 16, or 5 per cent, in patients with thyrocardiac disease; all the remaining cases (10 per cent) occurred in association with various other conditions. In order to compare this distribution and to determine whether or not these percentages differed from the natural grouping of cardiological patients, a sample of 5,530 patients with supraventricular paroxysmal tachycardia was analyzed which showed the following incidence: 1,188, or 21 per cent were normal; 1,698, or 31 per cent had arteriosclerotic heart disease; 935, or 17 per cent, had hypertensive heart disease; 915, or 16 per cent, had rheumatic heart disease; 199, or 4 per cent, had thyrocardiac disease; the remaining patients (11 per cent) had other varied cardiac conditions.

Of our 361 patients with supraventricular paroxysmal tachycardia there were 206 in whom the basal metabolic rate had been determined. Since the largest percentage of cases of supraventricular paroxysmal tachycardia occurred in normal persons and in those with rheumatic heart disease, these two groups were studied in regard to the basal metabolic rate. There were 97 persons in the normal group upon whom determinations of the basal metabolic rate had been made. In 4 of these, or 4 per cent, the rate was above +20; in 80, or 86 per cent, it was between +20 and −20; and in 10, or 10 per cent, it was below −20 per cent. There were 51 patients in the rheumatic heart disease group upon whom the determinations were made. In 2 of these, or 4 per cent, the rate was above +20; in 43, or 84 per cent, it was between +20 and −20; and in 6, or 12 per cent, it was below −20 per cent. Of all the subjects upon whom basal

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metabolism determinations were made, in 17, or 8 per cent, the rate was above +20; in 168, or 82 per cent, it was between +20 and −20; and in 21, or 10 per cent, it was below −20 per cent. It appeared from these studies that hyperthyroidism or hypothyroidism has no effect upon the occurrence of supraventricular paroxysmal tachycardia and that most attacks of this type of tachycardia occur in patients with rheumatic heart disease.

The high percentage of paroxysmal tachycardia found in the normal group is explained by the fact that these persons frequently presented themselves for examination because of the attacks of rapid heart action. In the sample group which revealed the ratio of various types of heart disease the incidence of normal persons was 25 per cent higher than that in the group with rheumatic heart disease. When this was considered it was realized that the occurrence of supraventricular paroxysmal tachycardia in association with rheumatic heart disease should be increased and that in the normal group it should be decreased from 34 per cent. The reverse was found in the group with arteriosclerotic heart disease, in which the incidence was 31 per cent, but only 14 per cent of these patients had supraventricular paroxysmal tachycardia. There appeared to be no definite relationship in occurrence between supraventricular paroxysmal tachycardia and either hypertensive or arteriosclerotic heart disease.

Conclusions

A review of 9,950 cases from a cardiologic service revealed an incidence of 3.6 per cent of supraventricular paroxysmal tachycardia.

The highest incidence (34 per cent) of supraventricular paroxysmal tachycardia was found in the patients with rheumatic heart disease and the next highest in those with normal hearts.

There was no relation found between supraventricular paroxysmal tachycardia and the other types of heart disease.

Hyperthyroidism or hypothyroidism had no effect upon the incidence of supraventricular paroxysmal tachycardia.

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A Slide Rule to Determine the Axis of the Electrocardiogram

By JOHN H. BEATTY, M.D.

A slide rule for determining the electrical axis of the electrocardiogram is presented. The device is a modification of the Dieuaide Chart. Construction of the slide rule and method of using it are described. Its use permits a very rapid calculation of the axis in degrees.

THE INCREASING use of the precordial and unipolar extremity leads has permitted new concepts and a fuller understanding of the electrocardiogram. The "electrical axis" as computed by the Einthoven triangle is receiving less and less attention. Recording the numerical value of the axis still, however, presents certain advantages, particularly in written descriptions of tracings, and in comparison of serial records. It is probable that the absence of a rapid uncomplicated method for measuring the axis in degrees has been one of the reasons for its omission from routine electrocardiographic interpretations. A simply constructed device is presented here which permits the determination of the numerical value of the axis with a minimum of time and effort.

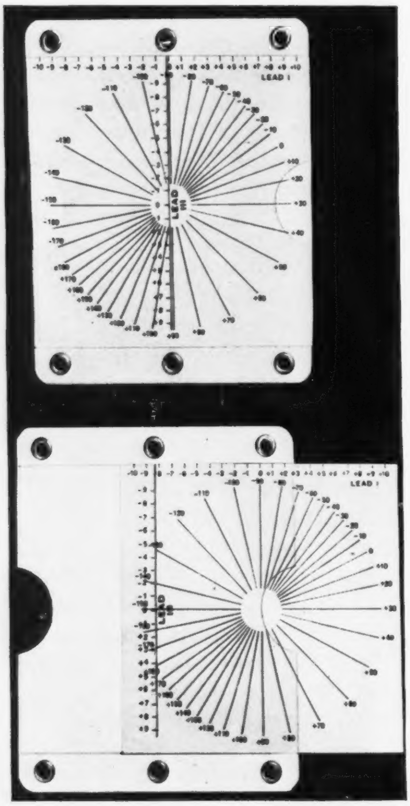

FIG. 1.—Slide rule for determination of the axis of the electrocardiogram.

From the Division of Medicine of the University of California Medical School, San Francisco, Calif.

The slide rule is based on the mathematical analysis and chart published by Dieuaide[1] in 1921. The chart is in general use and can be found in many of the standard texts. In effect, the chart alters the Einthoven triangle to the extent that the radial lines measuring the axis are related to rectangular coordinates. The slide rule facilitates the use of this chart to permit a considerably more rapid solution.

The slide rule (fig. 1) consists of two parts: (1) a square sliding panel and (2) a frame to which is attached a transparent vertical strip beneath which the panel moves. The radial lines of the Dieuaide Chart are drawn on the center panel with the zero directly to the right of the center of the dial. The ordinate scale of the chart, which represents the values for the deflection in Lead I, is placed across the top of the center panel. The abscissa scale is reproduced along the vertical center line drawn on the overlying transparent strip fixed to the frame. When the panel is in mid-position the vertical center line overlies (1) the center point of the dial, (2) the +90 and −90 points on the circumference of the dial, and (3) the zero or center point of the horizontal (Lead I) scale at the top of the panel.

Measuring the Axis

To find the numerical value for the axis, the algebraic sums of the deflections in Leads I and II are determined in the usual manner. The panel is then moved so that the value on the horizontal scale, equal to the deflection in Lead I, is under the vertical center line. The value for the Lead III deflection is then found on the vertical scale. This point overlies the labeled radial line which gives the axis deviation in degrees. Once the panel has been moved to the proper position, the value for the axis can be read directly. For example: if the value for Lead I is +6 and for Lead III is −4, the panel is moved to the left until the +6 on the horizontal scale is under the vertical line. Reading down the vertical scale, −4 is found to lie just above the radial line for −10 degrees, giving a value of −11 degrees.

So little time is required to make this determination that for the past two years it has been made a part of the routine electrocardiographic interpretations made at the University of California Hospital.

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A Quantitative Comparison of Unipolar and Augmented Unipolar Limb Leads

By Ernst Simonson, M.D., and Ancel Keys, Ph.D.

Goldberger has claimed that his augmented unipolar limb leads (aV) are identical—except for a 50 per cent larger amplitude—and interchangeable with Wilson's original V leads, but this claim was not supported by quantitative evidence. The advantage of larger amplitudes explains the increasing preference for the aV leads. A quantitative comparison between V and aV leads revealed such tremendous variability of the augmentation ratio, both interindividual and between leads in the same individual, that standards obtained with V leads are not applicable to aV leads and vice versa. V leads and aV leads are not interchangeable.

PROCEEDING from the Einthoven triangle theory of the electrocardiogram, Wilson and his collaborators[1] suggested that a relatively neutral reference electrode (T) could be obtained by pooling the three limb electrodes in a common terminal. Though the potential of such a terminal electrode is not zero, it is definitely smaller than the potential variations in any single limb electrode. In spite of the theoretic merit of Wilson's V lead, it has the disadvantage of occasional small magnitude of the deflections in the unipolar limb leads V_R, V_L, and V_F. In order to increase the amplitude of deflections, while still retaining the advantage of an "indifferent" reference electrode, Goldberger[2–4] modified Wilson's procedure by disconnecting the central terminal from the limb to which the exploring electrode was attached. Thus, Goldberger pools only two instead of three leads. By mathematical deduction he concluded that this procedure would augment the deflections by 50 per cent. This was expressed in the nomenclature "aV" leads, "a" indicating augmented. Expressed on a percentage basis, the unipolar aV limb leads would equal 150 per cent of the amplitudes in the unipolar V leads. Except for the larger amplitude, Goldberger claimed that the V and aV leads are identical and interchangeable. Goldberger also omitted the 5,000-ohm resistors placed between the extremity electrodes and Wilson's terminal (T); this, however, does not essentially affect the basic principle of augmentation.

The advantage of having larger amplitudes in the unipolar limb leads explains the recent tendency of electrocardiographers to use Goldberger's aV leads. The preference for aV rather than V unipolar leads is, however, not uniform. While Myers and Klein[5] prefer the Goldberger leads, Kossmann and his associates[6] discarded Goldberger's electrode because they sometimes observed considerable distortions compared with Wilson's three-lead terminal electrode. At times, however, Kossmann and his coworkers used Goldberger's two-lead pooling with Wilson's resistors; detailed comparisons were not reported for any of these arrangements. Although no objection can be made against the mathematical basis of the aV leads, the question of possible distortion can only be decided experimentally. Kisch[7] reported a case with grossly different augmentation in aV_R (162 per cent), aV_L (143 per cent) and aV_F (108 per cent) and implied that this is not unusual. In the absence of a quantitative comparison between the aV and V leads, the choice between them has been left mainly to subjective preference. This article reports a quantitative analysis of the augmentation obtained with aV limb leads.

Method

In a group of 20 normal men aged 20 to 53 years, in 2 patients with abnormal right axis deviation, and in 4 patients with abnormal left axis deviation, the standard leads, the

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V_R, V_L, V_F leads (Wilson leads), and the aV_R, aV_L, and aV_F leads (Goldberger leads) were taken with the Sanborn Viso-Cardiette. The exploring electrode was placed several inches from the nearest terminal of the "T" electrode. Previous to this work, a quantitative comparison of electrocardiograms obtained with a string galvanometer (Cambridge), an amplifier instrument (Sanborn), and the Viso-Cardiette was made. There was good agreement between the various instruments in regard to the recorded amplitudes of the deviations. In the Viso-Cardiette, the three limbs RA, LA and LL are connected to the V terminal each through a separate 5,000-ohm resistance. The Sanborn Company states that this arrangement in connection with the high-impedance amplifier input (around 500,000 ohms) reduces the error due to variable skin resistance to 0.2 per cent. It seemed therefore, that the Viso-Cardiette was well suited for this experimental study.

In each tracing, the amplitudes of the QRS complex and the T wave were averaged from at least five beats. The measurements were made as carefully as possible and were independently checked. In 10 of the subjects the aV leads were compared with and without 5,000 ohms in each branch of the central terminal; for this purpose shielded cables were used to pool the leads. In another group of 22 subjects (13 men, 9 women), the repeat variability of the RS amplitude in V_F was investigated with both Wilson and Goldberger leads. Finally, in 15 subjects, V_R and aV_R leads were also taken with the Cambridge electrocardiograph (string galvanometer).

Results

The amplitudes (positive or negative) of the QRS complex and of the T wave were plotted for all unipolar limb leads with the amplitudes in the V leads as abscissa (positive right, negative left) and the amplitudes in the aV leads (positive up, negative down) as ordinates. Thus, in figure 1, the right upper quadrant shows the R wave, the left lower quadrant shows the S wave.

The scatter diagrams for the various leads and deflections were similar, so that it is sufficient to show three diagrams (figs. 1–3) for illustration: the R and S waves for the left leg lead (fig. 1), the T wave for right arm lead (fig. 2), and the QS deflection for the right arm lead (fig. 3). Since the R wave in this lead is small or absent, only the negative deflection, Q or S, was plotted, with abscissa and ordinate increasing from left to right and upward. The 150 per cent slope, which corresponds to Goldberger's predicted augmentation over the Wilson leads, is indicated by a solid line. The figures show that the predicted slope agrees roughly with the general trend observed. However, the individual scatter is great. Theoretically, there is no reason to expect an effect of the axis or the direction of potentials on the augmentation in the aV leads, but nevertheless it should be investigated whether these factors determine the individual scatter and trend. It seems that the scatter or trend is not affected by the QRS axis within the normal limits. In figure 1, the values of the S wave in the 4 patients with abnormal left axis deviation are below the 150 per cent slope, and the R waves of the 2 patients with abnormal right axis deviation are above the 150 per cent slope. However, the scatter of the values of patients is within the range of normal scatter. In figure 2, the augmentation for two positive T waves, one of a patient with abnormal left axis deviation, and the other of a patient with abnormal right axis deviation, fall below the 150 per cent slope. In the V_L leads, the values of the patients were within the normal scatter (not included in figs.1–3). The QS waves of the right arm lead (fig. 3), representing mostly right ventricular cavity potentials, and the R wave in the left leg lead (fig. 1), mostly representing left ventricular epicardial potentials, show about the same general trend, and the same is true also for the R and S waves of the left arm lead (not included in figs. 1–3). Thus, it is our impression that trend and scatter are largely independent of QRS axis and the direction of deflections. This is of interest since the potential of the left ventricle (R wave as major deflection) might be recorded in the V_F *or* V_L lead, de-

pending on the position of the heart. The S wave was the major deflection in the V_L or aV_L leads in all cases with a QRS axis exceeding 64 degrees, and in the V_F or aV_F leads in all cases with a QRS axis less than 39 degrees.

Since the augmentation does not depend on the direction of the potential, it seemed to be justifiable to take the major QRS deflection in any given lead, whether R or S wave, as the basis for statistical evaluation. Small amplitudes involve a comparatively large error of measurement, which has been recently demonstrated in a quantitative way,[8] and the error in calculating percentages of augmentation with small amplitudes is so great that we discarded all amplitudes lower than 1 standardized mm. (= 0.1 mv) in the Wilson leads or 1.5 mm. in the Goldberger leads.

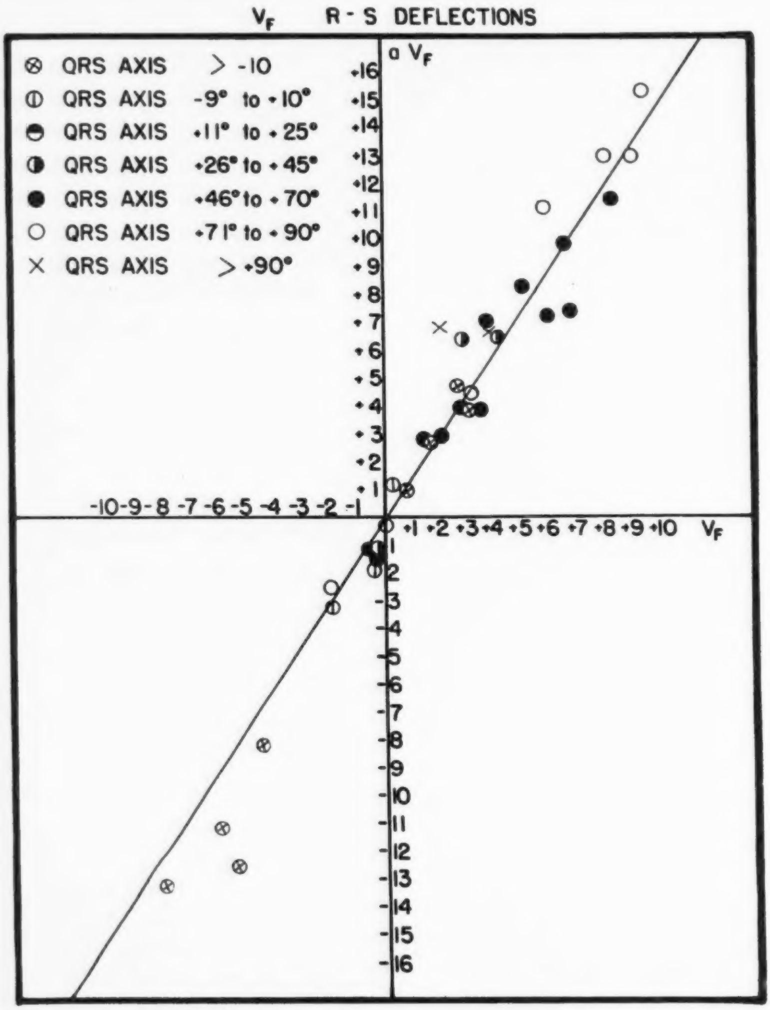

FIG. 1.—Amplitude of R S deflection in V_F (abscissa: positive right, negative left) versus aV_F (ordinata: positive up, negative down). The right upper quadrant shows the R wave; the left lower quadrant shows the S wave. The solid line corresponds to an augmentation factor for aV_F = 150 per cent of V_F. The individual QRS axis is indicated by symbols.

While figures 1–3 show that the slope agrees roughly with the predicted augmentation of 150 per cent, the validity of the aV leads as a clinical method must be determined by analysis of interindividual variability. Clinical electrocardiography is concerned with individual patients and not with groups.

Table 1 shows the means, interindividual variability of the augmentation expressed as standard deviation (S.D.), the expected normal range for 90 per cent population (calculated from the S.D.), and the number of values. In the QRS deflections the number of available values (those exceeding 1 mm. in the Wilson leads) equals or approaches 26 (the total number of subjects), while it is substantially smaller for the T wave in Leads V_L and V_F.

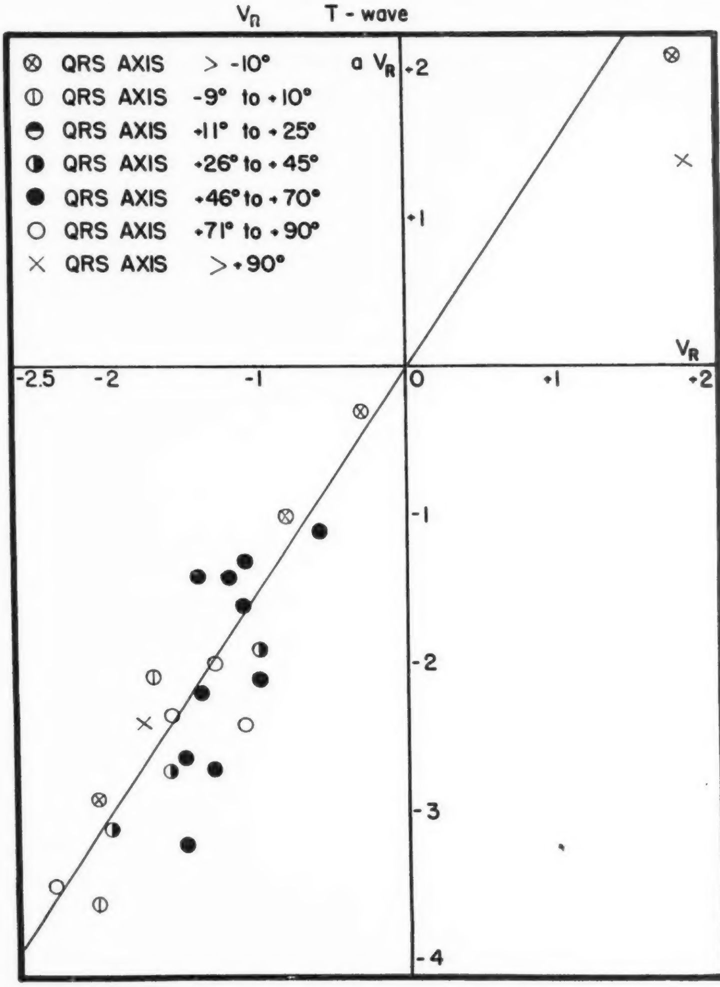

FIG. 2.—Amplitude of the T wave in V_R (abscissa: positive right, negative left) versus aV_R (ordinata: positive up, negative down). The solid line corresponds to an augmentation factor of aV_F= 150 per cent of V_F. The individual QRS axis is indicated by symbols.

In agreement with the impression gained from figures 1–3, the mean is fairly close to 150, except for Lead V_F (aV_F) in which there were

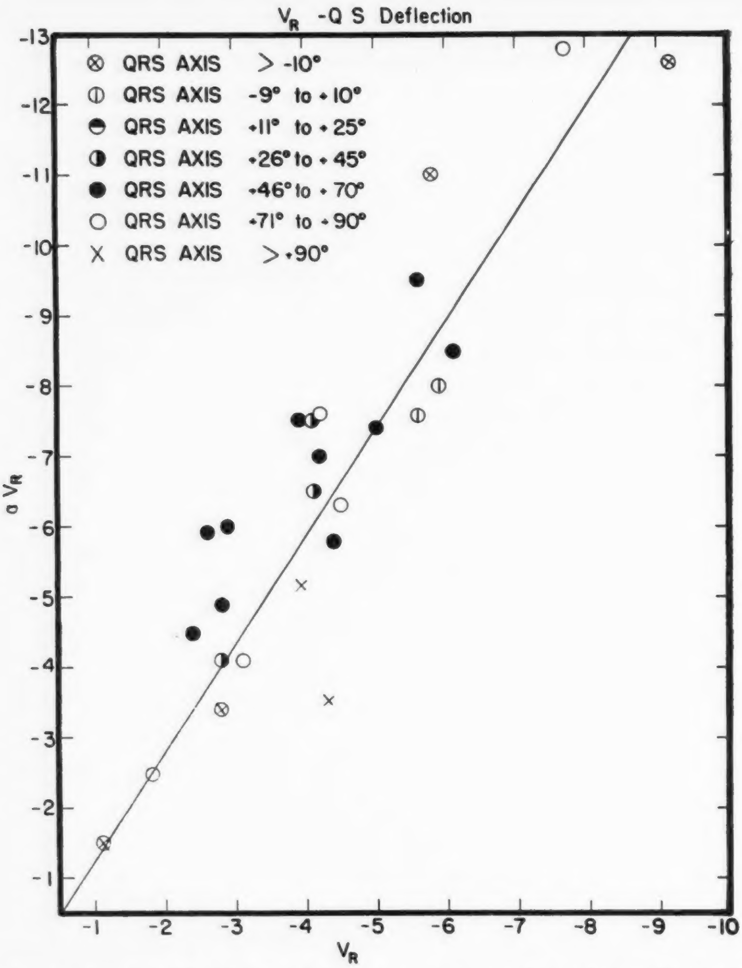

FIG. 3.—Amplitude of QS deflection in V_R (abscissa) versus aV_R (ordinate). The solid line corresponds to an augmentation factor of $aV_F = 150$ per cent of V_F. The individual QRS axis is indicated by symbols.

TABLE 1.—*Augmentation of Amplitudes in the Goldberger Leads (aV) Expressed as a Percentage of the Wilson Leads**

	$\frac{aV_R}{V_R} \times 100$		$\frac{aV_L}{V_L} \times 100$		$\frac{aV_F}{V_F} \times 100$	
	QRS	T	QRS	T	QRS	T
Mean	156	147	165	157	184	187
S.D.±	29.8	48.3	41.4	39.0	77.0	62.7
Expected upper limit†	205	220	233	221	311	290
Expected lower limit‡	107	100‡	100‡	100‡	100‡	100‡
Number of values	26	24	22	13	25	15

* The QRS or T deflection is compared in the same unipolar limb lead. Means and standard deviations for twenty-six subjects.

† The expected range refers to 90 per cent of the population.

‡ The lower limit of 100 is assumed where, according to the variability, the aV leads may show a smaller amplitude than the V leads.

means of 184 and 187 per cent, respectively, for the QRS complex and the T wave.

The variability, expressed by the standard deviation (S.D.) is very large. A predicted range was calculated for the accepted limit of statistical significance of P = ±5 per cent, which indicates the variability limits for 90 per cent of the population. A lower limit of 100 (equality of amplitude in the V and aV leads) was assumed when a lower value would have been obtained on the basis of the statistical calculation. It is not probable that the aV leads would show a smaller amplitude than the V leads; it must be assumed that the distribution curve is asymmetrical to the left. respectively), but in the left arm and left leg leads the S.D. of the augmentation of the T waves is the same as or even somewhat smaller than the S.D. of the QRS complex.

Another criterion for the use of Goldberger's method is the consistency of the augmentation between the various leads. This is expressed as the ratio of augmentation between two (aV) leads, again compared on a percentage basis. Equal augmentation between two leads would be indicated by a percentage of 100.

Table 2 shows that the mean percentage is close to 100, but the variability (S.D.) is as large as the interindividual variability of the augmentation in any single lead (table 1).

TABLE 2.—*Comparison of Augmentation with the Goldberger Leads (aV) in the Three Unipolar Limb Leads in the Same Subjects**

	Largest QRS Deflection			T wave	
	$\frac{aV_R/V_R}{aV_L/V_L} \times 100$	$\frac{aV_R/V_R}{aV_F/V_F} \times 100$	$\frac{L/V_L}{aV_F/V_F} \times 100$	$\frac{aV_R/V_R}{aV_L/V_L} \times 100$	$\frac{aV_R/V_R}{aV_E/V_E} \times 100$
Mean	98	106	99	100	94
S.D.±	26.5	47.6	48.5	36.6	35.2
Number of values	25	25	24	13	15
Expected upper limit†	142	184	179	160	152
Expected lower limit†	54	28	19	40	36

* Expressed as the ratio between leads on a percentage basis. A value of 100 would mean identical augmentation in the two leads compared.

† The expected range refers to 90 per cent of the population.

The expected range extends from 100 to 200 per cent augmentation or more. In other words, the augmentation obtained with the aV leads in any individual may lie anywhere between no augmentation at all and twofold or even threefold augmentation. In the remaining 10 per cent of the population the expected range would even be greater. This tremendous variability is not explained by or correlated with the mean amplitude of deflections; this means, indirectly, that it is not due to the error of measurement. The mean amplitude of the QRS deflections in V_R, V_L, and V_F was 4.3, 3.3, and 4.8 mm. respectively, and even larger in the aV leads. This is a magnitude which can be measured with reasonable accuracy. The mean amplitude of the T waves is much smaller (1.5, 1.2, and 1.3 for V_R, V_L, and V_F, In any single individual (in 90 per cent of the population), the ratios of the augmentation between the various leads may vary from 0.2 to 1.8. In other words, the relative augmentation in the different limb leads is completely erratic.

In our first series the leads were taken in the following sequence: V_R, aV_R; V_L, aV_L; V_F, aV_F. This might exaggerate the scatter of the augmentation ratio if there was spontaneous variability of electrocardiographic potentials within the short intervals between two successive leads. This seemed improbable, but it could not be excluded without test. In a former study[8] considerable day-to-day variability of several electrocardiographic items was observed. Ideally, the V and aV leads should have been recorded simultaneously. Since this is

technically impossible, the repeat variability of the RS wave in the V_F and aV_F leads was studied in the second series in the following sequence: V_F, aV_F, V_F, aV_F. The time intervals between the first and second V_F (or aV_F) lead corresponded closely to the time interval between the V and aV leads in our original procedure.

Twenty-two normal subjects were used for this second series (13 men and 9 women); ten of them had also served as subjects in the first series (Tables 1 and 2). The largest deflection (R or S) was taken as the basis for the calculation; this exceeded 1 mm. in the V_F leads and 1.5 mm. in the aV_F leads in all 22 subjects. The average amplitude of the RS deflection in the first V_F sample was 3.8 millimeters. The mean value of RS in the second recording of the V_F lead, expressed as a percentage of the first record, was 100.6, with a standard deviation of ± 5.8; the second recording of the aV_F lead averaged 98.9 per cent of the value in the first record of aV_F, with a standard deviation of ± 2.6. The variability is small and corresponds roughly to the magnitude of the error of linear measurement of the record.[8] This means that the variability of the augmentation in the aV_F leads cannot be explained by spontaneous physiologic variability of the amplitude in the time interval between two leads or by intrainstrumental variability.

We chose the V_F leads for this second comparison for two reasons: The standard deviation was higher than in the other leads (table 1), and the mean augmentation (184 per cent of the RS deflection and 187 per cent for the T wave) was substantially higher than Goldberger's predicted augmentation of 150 per cent. The additional series gave the opportunity to check this result.

In this second series the mean augmentation of the RS deflection in the aV_F lead was 193 per cent with a standard deviation of ± 57.1. The results are in good agreement with those shown in table 1. In order to test the statistical significance of the difference between actual and predicted augmentations, the F test was used for the total of 39 different subjects of both groups. For each subject only one determination was used. The mean difference between actual and predicted augmentation was +34.5 per cent (of V_F) practically identical with the value in table 1. The F value was 15.2, that is, above the level of 0.1 per cent chance probability. The difference between actual and predicted augmentation ratio in the aV_F leads is statistically highly significant.

Comparison of the aV leads with and without the 5,000-ohm resistance in ten subjects showed close agreement in the majority but occasionally larger differences were observed. Out of twenty-nine pairs of comparisons of the QRS complex for the three unipolar limb leads (the deflection in one subject in V_L was less than 1 mm. and was omitted for this reason), the agreement was within 10 per cent in eighteen, between 10 and 20 per cent in seven; the deviation exceeded 20 per cent in four comparisons. This distribution agrees fairly well with the recent observations of Bryant and associates.[9]

In 15 subjects, the V_R and aV_R leads were taken with the Cambridge Electrocardiograph (string galvanometer). The results obtained for the QS deflection (mean augmentation 157 per cent with a standard deviation of ± 24.9) were very similar to those obtained with the Viso-Cardiette (156 per cent ± 29.8, see table 1). This result agrees also with Rappaport and Williams'[10] conclusions that the unipolar limb leads will be accurately recorded by a string galvanometer if the contact resistances at the right arm, left arm, left leg, and exploring electrode do not exceed approximately 9,000 ohms. The variability of the augmentation ratio was about the same with and without the resistance.

Discussion

The results show such a degree of interindividual variability of the augmentation factor in the aV leads, both in single leads and between leads, that Goldberger's method appears to be unsuitable for any purpose in which comparison with the Wilson leads is to be made or implied. Clearly, standards obtained with the Wilson leads are not applicable to the Goldberger leads and vice versa, and these leads are not interchangeable.

The predicted range of variability in the augmentation applies, in a strict sense, to a population similar to that represented by our sample. There is no reason to expect essentially different results by enlarging the number of our experimental group, but the variability might be different in another group differently composed. Our group was rather homogeneous compared to the material in average hospitals. Since it is reasonable to expect an even greater variability in more heterogeneous groups, our data and estimates of the variability in augmentation in the Goldberger leads as compared with the Wilson leads are, if anything, conservative.

It is of interest to consider the possible reason for the discrepancy between the Wilson and the Goldberger leads. Since, according to Einthoven's theory, the algebraic sum of the potentials of all three limb leads should be zero, Goldberger[2–4] suggested that advantage be taken of the fact that the potential in any limb lead should equal the (negative) sum of the potentials of the two other leads. Thus, left arm (LA) potential + left leg (LL) potential = − right arm (RA) potential, and a similar relationship would hold for any other lead. The result would be, as Goldberger claims, that it should be possible to obtain a potential, augmented by 50 per cent, without distortion.

The present results show, however, that this expectation is not realized for individuals for any one of the unipolar limb leads and for the leg lead even the mean of a group of normal individuals does not conform to the simple theory. But the theoretical basis for both Wilson's and Goldberger's methods is the same. Obviously, there must be erroneous assumptions in the basic theory. Goldberger[4] clearly indicated these assumptions but did not offer any real proof of their validity. The crux of the theory is the assumption that the algebraic sum of the true absolute potentials for the recording positions on the three limbs is equal to zero. But if the potential at the V terminal is not actually zero, then Goldberger's calculation as to the augmentation obtained by his arrangement is invalid. Wilson and his collaborators[11] referred to the work of Eckey and Fröhlich[12] and of Burger[13] as showing that the departures from zero of the terminal (three lead) "do not ordinarily exceed 0.3 millivolt." However, Wolferth and Livezey[14] have criticized the validity of the procedure used by Eckey and Fröhlich and the most that one may say is that the resultant absolute potential at the V terminal is probably rather small in most cases. It should be pointed out, however, that a potential of 0.3 millivolt would be by no means negligible in view of the magnitude of the deflections in the unipolar limb leads.

Substantial arguments have been made for [12, 13, 15] and against[16, 17, 18] the validity of the Einthoven triangle theory. The situation seems to be that the Einthoven triangle theory is a useful approximation but that it cannot be applied with absolute rigor. It is necessary also to consider the variability of the skin resistance, as recently discussed by Rappaport and Williams.[10]

Consideration of the utility and meaning of so-called unipolar leads is impaired by such loose or misleading statements as "unipolar extremity leads are more accurate than the standard leads,"[4, p. 56] and that Goldberger's two-lead terminal is an "indifferent electrode of zero potential."[4, p. 28] It is true, for example, that V_R, or aV_R, is a more accurate estimate of the absolute potential at the right arm than could be obtained from the standard Leads I and II but, conversely, Lead I is a more accurate estimate of the difference between right and left arms than is gained from V_R, aV_R, V_L, or aV_L. And it can hardly be maintained that the Goldberger two-lead terminal is actually "indifferent" or has truly a "zero potential." Elsewhere,[19, p. 375] Goldberger admits the possibility that his "indifferent electrode" may not have a zero potential but goes on to argue that "the algebraic sum of the records obtained from the three extremities will equal zero." We have already noted the absence of experimental support for this statement.

It cannot be denied that there are important advantages in any system in which potentials are recorded so that they reflect primarily a single point of placement of the electrode rather than the difference between two points which may vary independently in potential.

We should, therefore, commend both Wilson's and Goldberger's procedures and should hope to see the older bipolar leads discarded eventually. But as between Wilson's and Goldberger's leads we see little theoretic basis for choice. In Goldberger's papers as well as in much of the present discussion the Wilson leads were used as the criterion for evaluating the Goldberger leads. The reason is mainly historical and stems from the fact that Wilson's leads have preceded those of Goldberger in time.

In view of our results it is surprising that Goldberger[19] attempted to use his method as a means of proving the validity of Einthoven's theory. He determined the greatest maximum and minimum deflections on the body surface with reference to the right arm. For this purpose, a wandering electrode was placed successively on a total of eleven points. The two points with the maximum positive and negative potentials were considered to represent a true indifferent electrode, and comparison was then made with Goldberger's aV leads. Goldberger claimed that these two methods yielded substantially identical results in 10 subjects, but offered only two examples of the electrocardiograms in lieu of numerical data. Unfortunately, the quality of the illustrations is very poor, but there appear to be several discrepancies between the records obtained with the two different electrodes.* More complete information of the results in the 8 other subjects would have been desirable. Goldberger argues that such "constancy" could not be a chance phenomenon, and therefore proves the validity of Einthoven's theory. He actually did not test whether the "agreement" is a coincidence or not. There are valid procedures to do so; for instance, other points with positive and negative potentials could be pooled as "indifferent" electrodes and compared on a quantitative basis.

Our results have no immediate bearing on the clinical usefulness of Goldberger's method. Normal standards could be developed for Wilson's or Goldberger's method, and results obtained on clinical material could be interpreted on the basis of such standards. But, as we have pointed out, standards for the V leads cannot be used for the aV leads. The clinical usefulness of either method can be decided only on the basis of large clinical experience. For the present, there is, in our opinion, no definite evidence for the superiority of the V or the aV leads. However, an agreement is desirable as to whether the V leads or the aV leads should be used. It would be confusing to have two similar, but not identical, procedures in use.

This laboratory is engaged in a long-range study on cardiovascular degeneration[20] involving the periodical investigation of about 400 normal subjects. We wanted to utilize this material for normal standards of the unipolar limb leads. The present study was mainly undertaken in order to arrive, for our own case, at a decision whether the V leads or the aV leads should be used. We have chosen the V leads because the only advantage of the aV leads is the larger amplitude, which can be as well obtained by a standardization of 15 mm. = 1 millivolt.

Summary

In 20 normal men and in 6 patients with abnormal axis deviation, the amplitudes of the QRS complex and the T wave in the three unipolar limb leads were taken with Goldberger's two-lead and Wilson's three-lead terminal. The mean augmentation obtained with Goldberger's method agrees fairly well with the predicted 150 per cent of the Wilson leads, except in Lead aV_F, where the mean is 184 (QRS complex) or 187 per cent (T wave). The high augmentation rate in aV_F was confirmed in another group of 22 subjects and was found to be highly significant.

The individual variability is so large that in 90 per cent of the population the augmentation

* In Case 1, the right arm lead taken with the control electrode (2 points with the maximum positive and negative deflection), shows a small, but definite S wave. In aV_R, there is only a notch which does not exceed the isoelectric line. In Case 2, the negative T wave of the left arm lead taken with the control lead is larger than the T wave in aV_L, while the T wave in the right-arm control lead seems to be smaller than the T wave in aV_R. The quotient R/S in the left leg, taken with the control lead, appears to be smaller than it is in aV_F.

may range from zero to two or even three times. The variability of the augmentation between the three unipolar limb leads in an average individual is about as large as the interindividual variability in any of the unipolar leads. The individual variability of the augmentation of aV_R was about the same when taken with the Viso-Cardiette or the Cambridge string galvanometer. The results show that Wilson's three-lead terminal and Goldberger's two-lead terminal are not interchangeable, and that standards obtained with one method are not applicable to the other method. The results have some bearing on the degree of validity of Einthoven's triangle hypothesis.

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Direct Electrocardiograms from the Human Heart in Situ. Comparison of Direct Leads with Precordial Leads

By Gordon E. Hein, M.D., and James C. Reavis, M.D.

The clinical value of multiple precordial leads has been proved abundantly and they are now used routinely in many electrocardiographic laboratories. The experimental background was based upon the correlation of precordial leads with direct leads in dogs. Direct leads from the surface of human hearts have rarely been reported. The present study is presented to add further justification to the use of precordial leads as "semidirect" leads in the human being.

THE OPPORTUNITY to obtain direct epicardial leads was provided when a patient developed constrictive tuberculous pericarditis while under observation in the hospital. Pericardiectomy was performed. During the operation the anterior surface of the heart was exposed widely by means of a sternum-splitting incision.

Direct leads from the surface of the human heart in vivo have been obtained by other workers. The first known report is that of Barker, Macleod, and Alexander.[1] In their subject the exposure of the heart was very limited and most of the sites from which tracings were obtained were identified by measurements correlated with the heart at autopsy. Their purpose was to measure the time of arrival of the excitatory impulse at various points on the surface of the heart. They also produced ectopic beats by electrical stimulation of points on the surface of the ventricles for studies of electrocardiographic determination of the site of origin of ventricular beats. They published only two of the direct epicardial tracings which they obtained and did not correlate these with leads overlying these portions of the heart on the chest wall. Feil,[2] in discussing electrocardiographic studies undertaken during pericardial resection for cardiac compression, stated that "electrograms in three cases showed greater voltage after resection of the scar and were typically monophasic." No tracings were shown and no mention of precordial leads was made. Nylin and Crafoord[3] took direct leads from two human hearts during thoracic surgery for pulmonary lesions. The pericardium was intact in both patients. They made no effort to correlate the direct leads with precordial leads.

Wilson and associates[4] have shown that in dogs there is a close correlation between direct and precordial leads. They have justified the use of the term "semidirect" leads in relation to the latter.

The purpose of the present paper is twofold. First, we wish to confirm the theory that there is a close correlation between direct and precordial leads for the human heart, and second, we wish to substantiate the statement that the characteristic electrocardiographic abnormality of chronic pericarditis, namely, the inverted T waves, is not due to pericardial disease per se.[5, 6] The direct leads were taken from the epicardium after the adherent and thickened pericardium and portions of the epicardium had been removed at surgery.

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Case Report

G. J., a Chinese-American student, aged 20 years, entered the hospital July 19, 1947, with complaints of progressive weakness, dyspnea, increased perspiration, sore throat, and a nonproductive cough, all having developed in the preceding three weeks. Entry physical examination revealed a temperature of 102 F. and a pulse rate of 132 per minute. There

were bronchovesicular breath sounds and bronchophony in the paravertebral region of the base of the left lung. No râles were heard. The apex beat was outside the left nipple line in the fifth intercostal space. The area of cardiac dullness was enlarged to the left. The heart was rapid but regular. The aortic second sound was louder than the pulmonic second sound. There was a pericardial friction rub, heard best along the left sternal border. The blood pressure was 115/80 in the right arm with the patient recumbent. The liver and spleen were not palpable. There was no ascites or edema. An x-ray film of the chest showed clear lung fields. The cardiac shadow was enlarged (transverse diameter 17 cm.). There was a leucocytosis (12,200 cells per cu. mm. of blood) with 71 per cent neutrophils. The sedimentation rate was 87 mm. per hour (Westergren). The electrocardiogram showed a flat T wave in Lead I, a low T wave in Leads II and IV, and a low, diphasic T wave in Lead III. There was slight elevation of the RS-T segment in Lead III. Reaction to a skin test with second test strength purified protein derivative tuberculin was 3+ in forty-eight hours. The tentative diagnosis of tuberculous pericarditis which was made was strengthened in the ensuing six months by the development of pleural effusions. Several thoracenteses were performed but *Mycobacterium tuberculosis* could not be recovered from the fluid by guinea pig inoculations.

Beginning on November 27, 1947, the patient was treated for four months with 1.0 Gm. of streptomycin daily. During this time it was noted that his heart size became normal and the friction rub disappeared, but the heart sounds became distant, the pulse pressure narrowed to 100/80, a paradoxic pulse appeared, and the liver became enlarged. Low voltage developed in all leads of the electrocardiogram (including the precordial leads). The venous pressure rose to 17.5 cm. of water and the circulation times for Decholin and ether became 32 seconds and 22 seconds respectively. Pleural fluid reaccumulated after thoracenteses. By December, 1947, it had become evident that the patient had developed constrictive pericarditis. Although the question of performing pericardiectomy was considered at that time, it was postponed because of the likelihood of active tuberculosis of the pericardium and pleura. By the latter part of April, 1948, it was apparent that the obstruction to blood flow was progressive and could not be improved by anything short of removal of the constriction about the heart. For this reason, pericardiectomy was performed on May 19, 1948, by Dr. Emile Holman.

Operative Procedure. Anesthesia was induced with cyclopropane. A curved incision was made over the sternum and epigastrium. The sternum was split up the center to the level of the second intercostal space and then transected at this level. The pleura was freed from the under surface of the sternum by blunt dissection and the sternum was spread by rib spreaders. Inspection showed a very quiet heart with minimal pulsations. The pleura was freed laterally on both sides of the pericardium. During this procedure, both pleural cavities were entered. The left was closed by sutures, but the right was left open to expose the base of the heart. The pericardium was incised and pericardial effusion under pressure was found. The fluid was aspirated. The incision was extended and showed a pericardium varying from 3 mm. to 1 cm. in thickness. Fibrous, granular material was present on the heart and pericardium. There were several tubercles in the pericardium, which was loosely adherent to the heart at the apex and along the venae cavae and other great vessels. By careful blunt and sharp dissection the pericardium was freed, exposing the pulmonary artery, the aorta, and both venae cavae. Around the venae cavae there were fibrous constrictions due to pericardial thickening. On freeing the pericardium around these vessels, the pulsations of the heart were noted to increase in amplitude and the patient's blood pressure rose slightly. It was noted that there was still some restriction of the heart due to epicardial thickening. The epicardium was incised and dissected away from part of the anterior surface of the right auricle and right ventricle. The danger of penetrating the heart was considered so great that further peeling was not attempted. At this point direct electrocardiographic leads were taken from the exposed surface of the heart. A mushroom catheter was then placed in the right pleural cavity. Two grams of streptomycin and 200,000 units of penicillin dissolved in 100 cc. of saline were placed in the operative site. The incision was closed, the lungs were reexpanded, and the patient was returned to the ward with a pulse rate of 90 per minute and a blood pressure of 110/70. During the operation he received intravenously 500 cc. of blood and 1000 cc. of 5 per cent glucose in normal saline.

Before induction of anesthesia the pulse rate was 110 per minute and the blood pressure was 90/70. During induction, the pulse rate rose to 120 per minute and the blood pressure fell to an imperceptible level. During most of the operation, which lasted three hours and ten minutes, the pulse rate remained 100 per minute and the blood pressure varied between 60/50 and 110/70. Respiration was maintained by means of the breathing bag during the two hours and thirty minutes that the chest was open. No irregularity of heart action was noted at any time and removal of the adherent pericardium and epicardium by blunt and sharp dissection caused no notable variation in cardiac rate or rhythm.

Pathologic examination of the excised pericardium showed "chronic granulomatous pericarditis consistent with tuberculosis." *Mycobacterium tuberculosis* was found in the fluid aspirated at operation by guinea pig inoculation.

Technic of Direct Electrocardiography. All leads were taken by Wilson's technic, making the exploratory lead positive and the indifferent lead negative. The indifferent lead was from Wilson's central terminal connected to the right arm, left arm, and left leg with 5000 ohms resistance in each limb.[4] The standardization was 10 mm. equals 1 millivolt in all tracings. The instrument used was a Sanborn "Cardiette" of the photographic type.

The precordial leads were taken in the routine manner while the patient was undergoing inhalation anesthesia on the operating table. The direct leads were taken by means of a sterilized standard precordial electrode held against the designated sites on the surface of the heart by the surgeon after the adherent pericardium had been completely dissected from the heart over its anterior surface. Only four direct leads were taken because the patient's pulse rate was high and his blood pressure was low during the entire operation and the surgical team was anxious to complete the operation and terminate anesthesia. Considering the vigorous movement of the denuded heart and the difficulty of exerting firm, even pressure against it, the base line was quite steady and the complexes were remarkably clear and similar in contour. In spite of numerous pieces of alternating-current electrical equipment in the operating room, no alternating-current artefact is seen in the direct leads, although it can be noted in the precordial leads.

Although we realize that a metallic electrode placed directly against the heart might conceivably give rise to injury potentials with changes in the QRS-T complexes, there is no evidence that such distortion occurred in this experiment and so far as we know, a standard precordial electrode has not been used previously in obtaining direct leads from the human heart.

Analysis of Direct Leads (Fig. 2)

Lead D_1. As shown in the right half of figure 1, this lead was taken from the anterior surface of the right auricle. The most prominent deflection is that of the P wave. After a very tiny upstroke there is a deep downward deflection which does not return sharply to the base line, but slurs upward throughout the last half of its duration. This creates the impression of a depressed "P-PQ junction," if such a term can be used in a sense analogous to that of the S-ST junction (J). Since the tuberculous infective process involved the auricles as well as the ventricles in our patient, the question arose whether this had the significance of an auricular "current of injury" analogous to an RS-T segment deviation in relation to the ventricles. In leads taken by Nylin and Crafoord[3] from the pericardium overlying a presumably normal right auricle, the P waves were sharp in contour and the P-R segments were isoelectric. Abramson, Fenichel, and Shookhoff[7] have suggested that deviation of the P-Q interval in auricular infarction is analogous to the de-

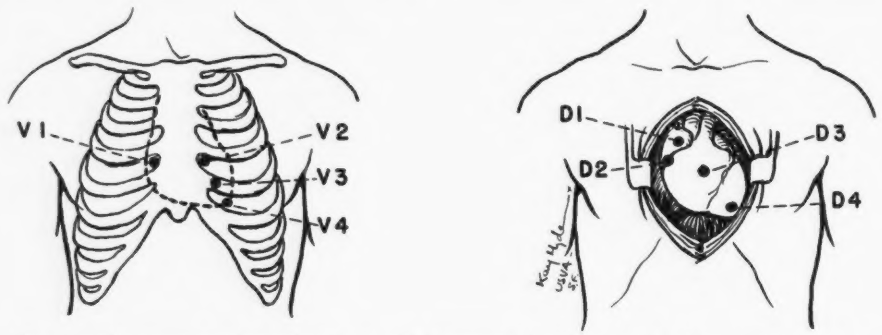

FIG. 1.—Diagrams showing points from which precordial and epicardial (direct) leads were obtained. *Left*: Precordial leads (preoperative); *Right*: Epicardial leads (immediately after pericardiectomy).

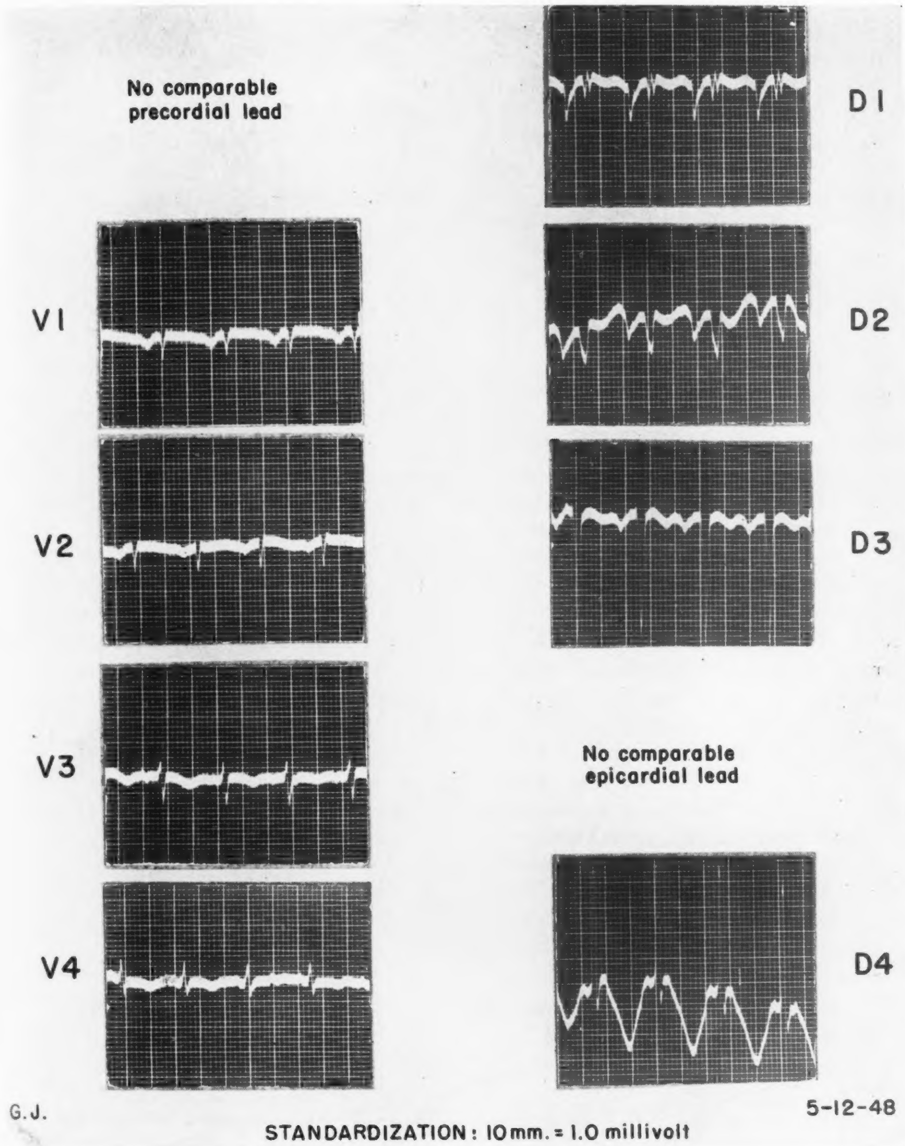

FIG. 2.—Precordial and epicardial (direct) electrocardiograms. (Left and right columns correspond to left and right diagrams in figure 1.)

viation of the RS-T interval which occurs in ventricular ischemia.

Some doubt, however, is cast on this interpretation by the esophageal lead studies of Brown.[3] He found a depressed P-R segment or slurred ascending limb of the auricular QS wave in leads taken near the left atrium of normal subjects.

The QRS complex consists of a prominent initial Q wave, a small R wave, and an S wave. The peak of the R wave is 0.04 second from the onset of the Q wave and indicates the

time of arrival of the wave of excitation at the nearby base of the right ventricle. The T wave is diphasic.

Lead D_2. This lead was taken from the lower portion of the anterior auriculoventricular sulcus. The P wave is somewhat less prominent and consists of a downward deflection. The same slurring of the upstroke is again present and has the same questionable significance as in D_1. The QRS complex consists entirely of a downward deflection which is notched at the bottom. The absence of a definite R wave probably indicates that the electrode is receiving a vector force mainly from the inside of the ventricular cup. The peak of the upward notch is 0.04 second from the beginning of the downward deflection, corresponding to the peak of the R wave in D_1, and thus probably indicates the activation time of the adjacent right ventricle. The T wave appears to be diphasic. The amplitude of the P wave is 4 millimeters. The amplitude of the QS wave is 7 millimeters.

Lead D_3. This lead was taken from the central portion of the anterior surface of the right ventricle (fig. 1). The P wave is distinct but much less prominent than in D_1 and D_2. It consists entirely of a downward deflection with the slurring still present on the upstroke, resembling, in this respect, the P wave in the preceding two leads. The QRS complex consists of a tiny upward deflection followed by a deep S wave. The upward deflection probably represents septal activation; no positive deflection suggestive of activation of the adjacent free ventricular wall can be seen. The T wave is slightly but definitely inverted in this lead. The amplitude of the S wave is 23 to 25 millimeters. The depth of the T wave is 1 to 2 millimeters.

Lead D_4. To obtain this lead the electrode was placed upon the anterior surface of the left ventricle as near the apex as was mechanically possible. A definite P wave cannot be made out, but there is an upward deflection preceding the QRS complex. This corresponds in position to the upward, slurred portion of the P-PR complex in the preceding three direct leads. The QRS complex consists of a tall R wave and a distinct S wave. The peak of the R wave follows the onset of the upward deflection by 0.05 second. The total duration of the QRS complex it 0.09 second. The S-T segment is isoelectric. The T wave is deeply inverted in this lead. The amplitude of the R wave is 24 millimeters. The amplitude of the S wave is 4 millimeters. The depth of the T wave is 13 millimeters.

Comparison of Direct and Precordial Leads

It can be seen by reference to figure 1 that D_2 corresponds in position to V_1, D_3 corresponds to V_2, and D_4 corresponds to V_4. There is no precordial lead taken at a point similar to D_1 and no direct lead taken at a point similar to V_3. Since the auricles have a much smaller muscle mass than the ventricles and are further from the chest wall, a comparable precordial lead cannot be obtained from any point on the precordium.

V_1 bears a general resemblance to D_2. The P wave is downward in both. The QRS complex consists of a QS wave only in both. The T wave in V_1 is flat rather than diphasic as in D_2. Finer points of the P and QRS complexes cannot be made out in the precordial lead because of low amplitude.

V_2 is similar to D_3 in that the P wave and major QRS deflection are downward in both. Details of the P wave cannot be made out in V_2. The tiny initial upward swing of the QRS in D_3 is not seen in V_2, and there is a tiny final upward deflection in the latter. The T wave in V_2 is flat rather than inverted as in D_3.

V_4 is similar to D_4 in contour. The P wave cannot be defined in either but there is a small upward swing in V_4 preceding the QRS complex at about the same interval as the similar deflection in D_4. The major deflection in both is the R wave and a smaller S wave is present in both. The RS-T segment is isoelectric in both leads. The T wave is inverted in both. The ventricular activation time is 0.04 second in both leads. In proportion to the R wave, the S in V_4 is deeper than the S in D_4. The depth of the T wave in V_4 is less in comparison to the R wave than it is in D_4.

Discussion

In general, the following similarities are noted: the QRS complexes in D_2, D_3, V_1, and

V_2 are all of right-ventricular type. D_4 and V_4 are left ventricular in type but there is an S wave in both and no Q wave is present in either. In the case of D_4 we know that the lead is entirely from the left ventricle. The absence of the septal Q wave may be due to end-on vector forces from the septum. The greater amplitude of all complexes in the direct leads is expected because of their proximity to the activated muscle mass.

The T-wave inversion, noted in the precordial leads preoperatively, is seen in the leads taken directly from the surface of the heart at operation. This inversion is taken as electrocardiographic evidence of pericarditis, but the direct leads substantiate the view that the inversion is not due to changes in the pericardium. Even the epicardium was absent at the site of D_3 and an inverted T wave is present. There can be little doubt that the abnormal process of repolarization is a function of damaged myocardium.

The correlation of direct and precordial leads in dogs is well established. Our findings confirm the close relationship in the human being. The minor differences between the direct and precordial leads are due, no doubt, to the influence of other portions of the myocardium on the leads more distant from the heart and to the intervening tissue. It is apparent, however, that the precordial leads are a semidirect approach to the study of excitation currents in the human heart as they are in the dog heart.

Summary

1. Direct leads were taken from a human heart widely exposed at surgery.

2. The direct leads, except for the markedly increased amplitude of all complexes, are generally similar to the V leads corresponding in position.

3. The inverted T waves, taken as evidence of "pericarditis" are due to changes in the underlying myocardium.

Acknowledgment

We wish to thank Dr. Emile Holman, Professor of Surgery, Stanford University School of Medicine, San Francisco, who performed the pericardiectomy, for his kindness and cooperation in this investigation.

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Electrocardiographic Changes in a Case of Left Ventricular and Septal Hypertrophy Resembling Anterior Myocardial Infarction

By Aaron Burlamaqui Benchimol, M.D., and Paul Schlesinger, M.D.

In certain instances of left ventricular hypertrophy, deep Q waves observed in the precordial electrocardiogram may resemble those of anterior myocardial infarction. Such a case is reported in a patient with syphilitic aortic insufficiency. Pathologic examination ruled out the diagnosis of infarction and revealed marked hypertrophy of left ventricular wall and the interventricular septum. The latter was of unusual degree and was probably responsible for the presence of large Q waves in precordial leads representing, the normal activation of the upper part of the interventricular septum which in cases of septal hypertrophy presumably originates a vector of greater magnitude.

THE PRESENCE of essentially negative QRS complexes displaying a QS configuration in right precordial unipolar leads has been observed in patients with uncomplicated left ventricular hypertrophy[1]; the absence of an initial *r* wave probably indicates a neutralization of the normal positivity in these leads by contralateral potential variations of greater magnitude owing to activation of the free wall of the enlarged left ventricle.

These changes are frequently indistinguishable from those due to a healed anteroseptal infarction, particularly in the absence of a positive clinical history or of serial tracings showing the characteristic RS-T and T-wave changes during the acute and subacute stages of coronary occlusion. In leads from the left side of the precordium, Q waves are usually recorded and are due to early activation of the interventricular septum from left to right; the presence of these deflections may occasionally give rise to a problem of differential diagnosis, anterolateral infarctions being suspected particularly when the Q waves are abnormally large. Wilson and associates[1] have pointed out that the R-wave amplitude decrease, or disappearance of this deflection as the exploring electrode is moved from the right to the left side of the precordium, may be considered as more reliable criteria for the electrocardiographic diagnosis of anteroseptal infarction than is the complete absence of R waves in all right precordial leads.

In a study of the electrocardiographic and pathologic findings in 20 patients with anteroseptal infarction, Myers, Klein, and Stofer[2] observed 8 subjects whose electrocardiograms showed an initial R wave of normal amplitude in Lead V_1 and abnormal QRS complexes of the QR or QS type in one or more of the following three precordial leads; in 5 patients all leads from the right side of the precordium displayed essentially negative QRS deflections. Although definitely abnormal Q waves were not found in Leads V_5 and V_6, there were two instances in which the amplitude of the initial negative deflection in these leads was at the upper limit of normal. This configuration was regarded as the transmission of the potential variations of the anteroseptal infarct to the left axilla due to marked clockwise rotation of the heart.

In addition to the absence of R waves in Leads V_1 to V_4 which occurs quite frequently in patients with marked left ventricular hypertrophy, we have observed several instances in which an initial upstroke was present in Lead V_1 and decreased in amplitude as the exploring electrode was moved from this lead to V_4; in occasional tracings, deep Q waves were recorded in Leads V_5 and V_6. In a recent publication, Quintiliano de Mesquita[3] reports

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a case of marked left ventricular hypertrophy with large Q waves in Lead CF_4 in which the abnormal configuration was interpreted not as an evidence of myocardial infarction but as a transition complex associated with an intraventricular conduction defect although pathologic examination was not obtained.

A definite diagnosis is often difficult to establish in these cases particularly in the absence of a positive clinical history; although the presence of infarction was considered highly improbable in our cases, its possibility could not be excluded merely on a clinical basis, particularly since all electrocardiographic criteria for the diagnosis of old anterior infarction in precordial leads were observed.

In a patient with aortic insufficiency and marked left ventricular hypertrophy who has recently come under our observation, the electrocardiogram was extremely suggestive of anterior myocardial infarction in view of the decrease in amplitude of the R wave from V_3 to V_4 in addition to the presence of an abnormally large Q wave in Lead V_6. Since no evidence of myocardial infarction could be demonstrated at autopsy despite a careful pathologic examination, a report of this case was considered to be of interest, from the electrocardiographic standpoint, investigating the possibility of interpreting the QRS changes in precordial leads as due to left ventricular and septal hypertrophy. It is our object in this article to suggest caution in the electrocardiographic diagnosis of anterior myocardial infarction in certain patients with left ventricular hypertrophy. Although such electrocardiographic patterns do not seem to be of frequent occurrence in these patients, Myers and collaborators[2] have recently emphasized the difficulty in the interpretation of tracings showing respiratory variations in the configuration of the QRS complexes in precordial leads simulating those due to anteroseptal infarction; furthermore, a patient is mentioned, who as yet has not been reported, whose electrocardiogram showed an initial R and a deep S wave in Leads V_1 and V_2 and a Q wave varying from 2 to 5 mm. in Lead V_4, followed by an R deflection which also varied in amplitude. Autopsy revealed both left and right ventricular hypertrophy but no evidence of infarction.

Case Report

S. S. V., a 47 year old Negro mechanic with syphilitic aortic insufficiency, was admitted to the hospital on August 16, 1948, with advanced congestive heart failure. He had been in good health until three years prior to admission when he first noticed dyspnea on exertion, orthopnea, palpitation, and ankle edema which later became generalized. Since that time he complained of constant pain in the left lower portion of his back and in the lumbar region. He was treated by a local physician and obtained relief from these symptoms which had recently recurred. At the age of 26 years, he contracted gonorrhea, but denied ever having had a chancre, although reactions to serologic tests for syphilis had been repeatedly positive in spite of antisyphilitic therapy.

Fig. 1.—Teleroentgenogram of the chest showing marked cardiac enlargement predominantly of the left ventricle and increased hilar markings.

Admission examination revealed a severely dyspneic patient with Cheyne-Stokes respiration and long periods of apnea during which the patient became markedly agitated. There were typical signs of aortic regurgitation, including an average blood pressure reading of 240/40 with marked fluctuations to the extremes of 300 systolic and 0 diastolic levels.

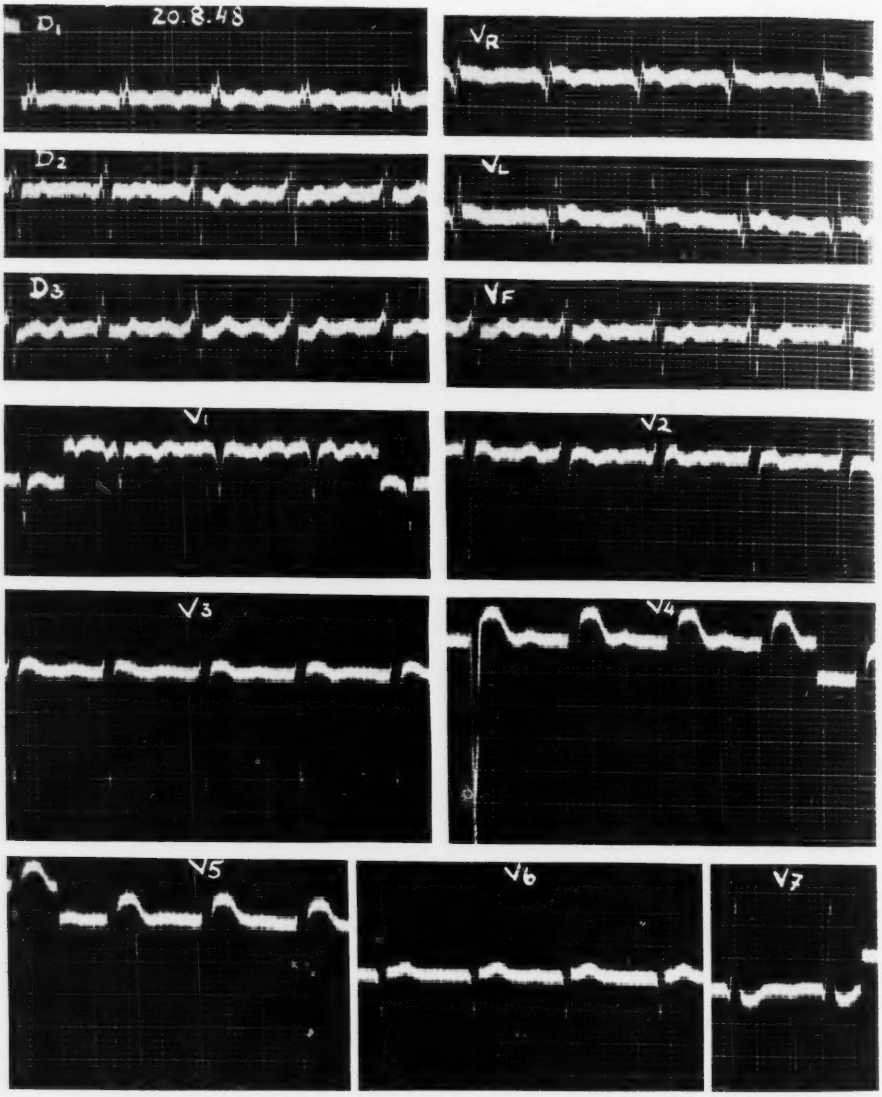

FIG. 2.—Electrocardiogram made shortly after the patient's admission showing auricular fibrillation with a slightly irregular ventricular rate of 107 per minute. Precordial leads taken at half normal sensitivity revealed left ventricular hypertrophy in addition to a decrease in amplitude of the R wave in Leads V_3 to V_5 and a deep Q wave in Lead V_6. The RS-T segment is elevated in Leads V_4 and V_5 and depressed in Lead V_7. The tracing is diagnostic of left ventricular hypertrophy and suggestive of anterior myocardial infarction and digitalis effect.

The heart was enlarged and a gallop rhythm was audible. The rate was 104 per minute, and the rhythm was slightly irregular. The liver was enlarged and tender to palpation. Râles were present at both lung bases. There was generalized edema.

Laboratory studies showed the following: Positive serologic reactions (to Kahn and Kline tests), a moderate amount of albumin in the urine, the specific gravity of which was 1.012; blood urea value of 70 mg. per 100 cc.; creatinine value of 1.3 mg. per

100 cc.; 16,750 white blood cells per cu. mm. of blood, with 92 per cent neutrophils; total serum protein of 6.1 grams per 100 cc., with 3.54 grams albumin, 2.56 grams globulin, and an index of 1.3; x-ray film of the chest obtained on April 28, 1948, in the outpatient department (fig. 1) showing marked cardiac enlargement particularly of the left ventricle in addition to a dilatation of the aorta. Diffuse atheromatosis of the abdominal aorta was demonstrated radiologically with no evidence of erosion of the lower thoracic or lumbar vertebral bodies. An electrocardiogram made shortly after admission (fig. 2) showed auricular fibrillation with a slightly irregu-

FIG. 3.—Pathologic specimen showing a transverse section of the heart which reveals a marked degree of left ventricular hypertrophy in addition to a greatly thickened interventricular septum which bulges into and reduces the capacity of the right ventricle. VE = left ventricle; VD = right ventricle

lar ventricular rate of 107 per minute, slurred QRS complexes, and signs of marked left ventricular hypertrophy in precordial leads. There was a decrease in the size of the R wave from V_3 to V_5 and a deep Q deflection in Lead V_6. The RS-T segment was elevated in Leads V_4 and V_5 and depressed in Lead V_7. The tracing was strongly suggestive of anterior myocardial infarction mainly in view of the characteristic QRS changes, since the alterations in RS-T segment and T waves could be attributed, at least partially, to the effects of digitalis. High precordial leads were essentially similar to those obtained at the usual levels. It is likewise conceivable that incomplete left bundle branch block could be indicated in this tracing notwithstanding the presence of a deep Q wave in Lead V_6 and a smaller initial negative deflection in Lead V_7, which, according to Sodi-Pallares,[4] could be explained by the location of the block below the origin of the initial vector of septal activation. In one electrocardiogram this type of block was suggested by the configuration of Lead I showing a slurred upstroke of the R wave which is strikingly similar to the tracings obtained experimentally by Sodi-Pallares and coworkers.

A progressively downward course was observed in spite of intensive therapy consisting of cardiotonic drugs, diuretics, and sedatives. The patient died five days after an episode of pulmonary embolism following a shocklike condition associated with an irregular cardiac rhythm. The electrocardio-

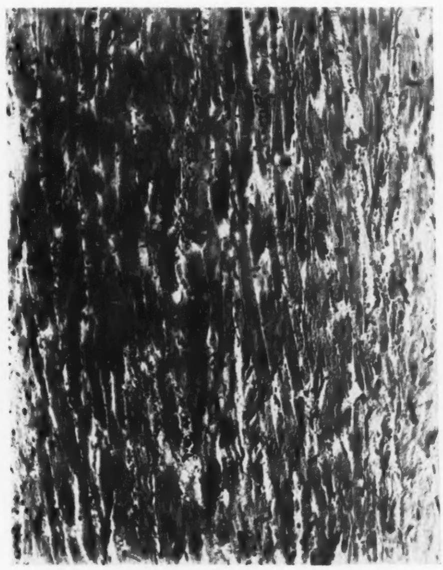

FIG. 4.—Histologic section showing the normal aspect of the myocardial fibers. Essentially similar sections were obtained at other points such as the interventricular septum, the cardiac apex, and the anterior wall of the left ventricle.

gram recorded a half hour before death showed a return to sinus rhythm with periods of bradycardia alternating with sinus tachycardia and partial A-V block with sinus depression.

Pathologic examination by Dr. Penna de Azevedo revealed the following: Syphilitic aortitis, syphilitic aortic valvulitis with deformity of the valves, aneurysmal dilatation of the thoracic aorta, edema and passive hyperemia with hemorrhagic infarcts in both lungs, cardiac hypertrophy, bilateral healed renal infarcts with atrophy of the kidneys, moderate ascites, and chronic bilateral fibrous pleuritis. The heart measured 13.5 by 7.5 by 8.0 centimeters. The left chambers showed a greatly increased capacity. The right ventricular chamber was markedly decreased in size and the extremely hypertrophied (25 mm.) interventricular septum bulged into the

cavity of the right ventricle (fig. 3). The inner aspect of the aorta showed marked irregularities due to yellowish plaques, some of which were calcified, alternating with large areas of tissue retraction. The coronary arteries were patent throughout. The myocardium was of firm consistency and of a dark red color with no apparent increase of fibrous tissue.

The wall of the left ventricle measured 26 mm. from endocardium to epicardium. Just above the diaphragm in the thoracic cavity there was an aneurysmal dilatation, 7.5 by 5.5 cm., to the left of the aorta with which it communicated through an orifice 2 cm. in diameter; the renal arteries were seen to emerge immediately below the aneurysm.

A number of histologic sections of the myocardium were made (fig. 4), particularly from those areas where the electrocardiogram suggested the possibility of infarction; no evidence of this type of lesion in its acute or chronic stage could be found.

Discussion

Since the electrocardiographic diagnosis of myocardial infarction was not confirmed at autopsy there did not seem to be a correlation between the tracings and the pathologic findings in this case.

The possibility of a very recent infarct in which the electrocardiographic changes may precede the histologic lesions in the myocardium as shown by Blumgart and associates,[5] and confirmed clinically by others,[2] was discarded in this patient, since not only were the coronary arteries found to be patent at autopsy but also because the patient died seven days after the tracings were obtained, a period of sufficient length for pathologic changes to occur.

The finding at autopsy of an extremely thickened interventricular septum bulging into the right ventricular cavity (anatomic stage of Bernheim's syndrome) suggested the possibility that the initial activation of the upper part of the hypertrophied septum could originate a septal vector of greater magnitude than that of the normal Q wave. According to this interpretation, the deep Q waves recorded in the left precordial leads in this case reflect early activation from left to right of the interventricular septum such as occurs in normal individuals although of greater voltage owing to septal hypertrophy.

The decrease in the amplitude of the R wave from Leads V_3 to V_5 is more difficult to explain according to the foregoing interpretation.

Several other explanations may be offered for the presence of abnormal Q waves in left precordial leads in the absence of infarction. Among these is the possibility that the QR complexes represent mixed cavity and epicardial potentials recorded in these leads as a result of cardiac rotation.

Summary and Conclusions

A case history is presented of a patient, with syphilitic aortic insufficiency and marked left ventricular hypertrophy, in whom the electrocardiogram was extremely suggestive of anterior myocardial infarction which was not found to be present at autopsy. Pathologic examination revealed marked hypertrophy of the left ventricle in addition to great enlargement of the interventricular septum which bulged into the right ventricular cavity reducing the capacity of this chamber.

It is suggested that septal forces from left to right of great magnitude could presumably explain the electrocardiographic findings in the absence of infarction.

On the basis of this case and previous ones without pathologic basis, the authors suggest caution in the electrocardiographic diagnosis of anterior myocardial infarction in the presence of marked left ventricular hypertrophy, particularly in patients with a negative clinical history.

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Aids for Determining Magnitude and Direction of Electric Axes of the Electrocardiogram

By Charles E. Jackson, Captain, M.C., U.S.A., and Travis Winsor, M.D.

Tables are presented which serve to facilitate the determination of magnitudes and directions of the electrical axes of various waves and segments of the electrocardiogram (P, QRS, RS-T, T and G). The tables may be used with the standard or unipolar limb leads. Normal values for the magnitudes and directions of certain vectors are presented.

In 1913, Einthoven, Fahr, and de Waart[1] described the method for determining the electric axes of the electrocardiogram. Wilson, MacLeod, Barker, and Johnston[2] described the index of the ventricular gradient which necessitated the calculation of the magnitude and direction of these axes. Ashman and his group[3-7] and Bayley[8] have extended our knowledge concerning the relationship between the various electric axes of the heart (P, QRS, initial portion of QRS, RS-T, T and G). It is the purpose of this report to present tables and a chart which facilitate the determination of the magnitude and direction of these axes.

The tables were developed (tables 1–4) by the use of a mechanical triaxial reference system and were checked using the formula for direction: tangent angle alpha $= \dfrac{2e_3 + e_1}{e_1\sqrt{3}}$. The magnitudes were determined using the formula: $E = \dfrac{e_1}{\text{cosine alpha}}$.[1] The values obtained were further checked by utilizing figure 1.

The magnitudes and directions are determined from the tables, using either the amplitudes in millimeters or tenths of millivolts, or areas in microvolt seconds or 4 microvolt second units. Leads I and III are employed in the determinations. To determine the electric axes from the unipolar limb leads, V_L should be substituted for Lead I and V_F for Lead III. Thirty degrees are subtracted algebraically from the angle obtained. The magnitude may be multiplied by 1.732 to obtain a magnitude comparable to that obtained from the standard limb leads.[9] For determining the magnitude and direction of the augmented unipolar leads, aV_L is substituted for Lead I and aV_F for Lead III. Thirty degrees is also subtracted algebraically. The magnitude in this case must be multiplied by $\dfrac{1.732}{1.5}$ to obtain magnitudes comparable to those obtained with the standard limb leads.

An alternative method for using the tables with curves of unipolar leads is to subtract V_R from V_L to obtain the value of Lead I and subtract V_L from V_F for the value of Lead III using the tables as suggested for the standard limb leads with no further correction. Similarly with the augmented unipolar leads, two-thirds of the value of aV_R is subtracted from two-thirds of the value of aV_L to obtain Lead I and two-thirds of the value of aV_L is subtracted from two-thirds the value of aV_F to obtain the value for Lead III using the tables as with the standard limb leads without further correction.

Figure 1 is employed with potentials obtained from Lead I and Lead III, using either amplitudes or areas. To employ the chart using amplitudes, the algebraic sum of the positive and negative waves in Lead I is plotted on the Lead I line. A similar procedure is carried out with Lead III. The lines perpendicular to the lead line at these points are followed to their intersection. The direction is found by connecting the center of the system with this intersection. The circle passing through

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this point gives the magnitude. To determine the electric axes from the unipolar limb leads from the chart, V_L should be substituted for Lead I and V_F for Lead III. Thirty degrees is subtracted algebraically from this angle. The magnitude may be multiplied by 1.732 to obtain a magnitude comparable to that obtained from the standard limb leads. For determining the magnitude and direction of the augmented limb leads, aV_L is substituted for Lead I and aV_F for Lead III. Thirty degrees is also subtracted algebraically. The magnitude in this case must be multiplied by $\frac{1.732}{1.5}$ to obtain magnitudes comparable to those obtained from the standard limb leads. The alternative method suggested for the unipolar and augmented unipolar leads in the preceding paragraph may also be used with the chart.

Normal values for the mean manifest electric

TABLE 1.—*Magnitude and Direction of Electric Axis when Lead I Is Positive and Lead III Positiv*

LEAD I

LEAD III	0.0	+0.5	+1.0	+1.5	+2.0	+2.5	+3.0	+3.5	+4.0	+4.5	+5.0	+6.0	+7.0	+8.0	+9.0	+10.0	+11.0	+12.0	+13.0	+14.0	+15.0	+20.0	LEAD III
0.0		.6 30°	1.2 30°	1.7 30°	2.3 30°	2.9 30°	3.5 30°	4.0 30°	4.6 30°	5.2 30°	5.8 30°	6.9 30°	8.1 30°	9.2 30°	10.4 30°	11.5 30°	12.7 30°	13.9 30°	15.0 30°	16.2 30°	17.3 30°	23.1 30°	0.0
+0.5	.6 90°	1.0 60°	1.5 49°	2.1 44°	2.6 41°	3.2 39°	3.8 38°	4.4 37°	4.9 36°	5.5 35°	6.1 35°	7.2 34°	8.4 33°	9.6 33°	10.7 33°	11.9 32°	13.0 32°	14.1 32°	15.3 32°	16.4 32°	17.6 32°	23.5 32°	+0.5
+1.0	1.2 90°	1.5 71°	2.0 60°	2.5 53°	3.1 49°	3.6 46°	4.2 44°	4.7 42°	5.3 41°	5.9 40°	6.4 39°	7.6 38°	8.7 37°	9.9 36°	11.0 35°	12.2 35°	13.3 34°	14.5 34°	15.6 34°	16.8 33°	17.9 33°	23.8 32°	+1.0
+1.5	1.7 90°	2.1 76°	2.5 67°	3.0 60°	3.5 55°	4.0 52°	4.6 49°	5.1 47°	5.7 45°	6.3 44°	6.8 43°	7.9 41°	9.1 39°	10.2 38°	11.4 38°	12.5 37°	13.7 36°	14.8 36°	16.0 36°	17.1 35°	18.2 35°	24.0 33°	+1.5
+2.0	2.3 90°	2.6 79°	3.1 71°	3.5 65°	4.0 60°	4.5 56°	5.0 53°	5.6 51°	6.1 49°	6.7 47°	7.2 46°	8.3 44°	9.5 42°	10.6 41°	11.7 40°	12.9 39°	14.0 38°	15.1 38°	16.3 37°	17.4 37°	18.6 36°	24.3 35°	+2.0
+2.5	2.9 90°	3.2 81°	3.6 74°	4.0 68°	4.5 64°	5.0 60°	5.5 57°	6.0 54°	6.6 52°	7.1 51°	7.6 49°	8.7 47°	9.9 45°	11.0 43°	12.1 42°	13.2 41°	14.4 40°	15.6 39°	16.7 39°	17.8 38°	19.0 38°	24.7 36°	+2.5
+3.0	3.5 90°	3.8 82°	4.2 76°	4.6 71°	5.0 67°	5.5 63°	6.0 60°	6.5 57°	7.0 55°	7.5 53°	8.1 52°	9.2 49°	10.3 47°	11.4 45°	12.5 44°	13.6 43°	14.7 42°	15.9 41°	17.1 40°	18.2 39°	19.3 39°	25.0 37°	+3.0
+3.5	4.0 90°	4.4 83°	4.7 78°	5.1 73°	5.6 69°	6.0 66°	6.5 63°	7.0 60°	7.5 58°	8.0 56°	8.6 54°	9.6 51°	10.7 49°	11.8 47°	12.9 46°	14.0 44°	15.2 43°	16.3 42°	17.4 42°	18.5 41°	19.7 40°	25.4 38°	+3.5
+4.0	4.6 90°	4.9 84°	5.3 79°	5.7 75°	6.1 71°	6.6 68°	7.0 65°	7.5 62°	8.0 60°	8.5 58°	9.0 56°	10.1 53°	11.1 51°	12.2 49°	13.3 47°	14.4 46°	15.5 45°	16.7 44°	17.8 43°	18.9 42°	20.0 42°	25.7 39°	+4.0
+4.5	5.2 90°	5.5 85°	5.9 80°	6.3 76°	6.7 73°	7.1 69°	7.5 67°	8.0 64°	8.5 62°	9.0 60°	9.5 58°	10.5 55°	11.6 53°	12.7 51°	13.7 49°	14.8 48°	16.0 47°	17.1 45°	18.2 44°	19.3 43°	20.4 43°	26.1 40°	+4.5
+5.0	5.8 90°	6.1 85°	6.4 81°	6.8 77°	7.2 74°	7.6 71°	8.1 68°	8.6 66°	9.0 64°	9.5 62°	10.0 60°	11.0 57°	12.1 55°	13.1 52°	14.2 51°	15.3 49°	16.4 48°	17.5 47°	18.6 46°	19.7 45°	20.8 44°	26.4 41°	+5.0
+6.0	6.9 90°	7.2 86°	7.6 82°	7.9 79°	8.3 76°	8.7 73°	9.2 71°	9.6 69°	10.1 67°	10.5 65°	11.0 63°	12.0 60°	13.0 57°	14.0 55°	15.1 53°	16.2 52°	17.2 50°	18.3 49°	19.4 48°	20.5 47°	21.6 46°	27.2 43°	+6.0
+7.0	8.1 90°	8.4 87°	8.7 83°	9.1 81°	9.5 78°	9.9 75°	10.3 73°	10.7 71°	11.1 69°	11.6 67°	12.1 65°	13.0 63°	14.0 60°	15.0 58°	16.0 56°	17.1 54°	18.2 53°	19.2 51°	20.3 50°	21.4 49°	22.5 48°	28.0 44°	+7.0
+8.0	9.2 90°	9.6 87°	9.9 84°	10.2 82°	10.6 79°	11.0 77°	11.4 75°	11.8 73°	12.2 71°	12.7 69°	13.1 68°	14.0 65°	15.0 62°	16.0 60°	17.0 58°	18.0 56°	19.1 55°	20.1 53°	21.2 52°	22.3 51°	23.4 50°	28.8 46°	+8.0
+9.0	10.4 90°	10.7 87°	11.0 85°	11.4 82°	11.7 80°	12.1 78°	12.5 76°	12.9 74°	13.3 73°	13.7 71°	14.2 69°	15.1 67°	16.0 64°	17.0 62°	18.0 60°	19.0 58°	20.0 57°	21.1 55°	22.1 54°	23.2 53°	24.2 52°	29.7 48°	+9.0
+10.0	11.5 90°	11.9 88°	12.2 85°	12.5 83°	12.9 81°	13.2 79°	13.6 77°	14.0 76°	14.4 74°	14.8 72°	15.3 71°	16.2 68°	17.1 66°	18.0 64°	19.0 62°	20.0 60°	21.0 58°	22.0 57°	23.1 56°	24.1 54°	25.2 53°	30.6 49°	+10.0
+11.0	12.7 90°	13.0 88°	13.3 86°	13.7 84°	14.0 82°	14.4 80°	14.7 78°	15.2 77°	15.5 75°	16.0 73°	16.4 72°	17.2 70°	18.2 67°	19.1 65°	20.0 63°	21.0 62°	22.0 60°	23.0 59°	24.0 57°	25.1 56°	26.1 55°	31.4 50°	+11.0
+12.0	13.9 90°	14.1 88°	14.5 86°	14.8 84°	15.1 82°	15.6 81°	15.9 79°	16.3 78°	16.7 76°	17.1 75°	17.5 73°	18.3 71°	19.2 69°	20.1 67°	21.1 65°	22.0 63°	23.0 61°	24.0 60°	25.0 59°	26.0 57°	27.0 56°	32.3 52°	+12.0
+13.0	15.0 90°	15.3 88°	15.6 86°	16.0 84°	16.3 83°	16.7 81°	17.1 80°	17.4 78°	17.8 77°	18.2 76°	18.6 74°	19.4 72°	20.3 70°	21.2 68°	22.1 66°	23.1 64°	24.0 63°	25.0 62°	26.0 60°	27.0 59°	28.0 58°	33.2 53°	+13.0
+14.0	16.2 90°	16.4 88°	16.8 87°	17.1 85°	17.4 83°	17.8 82°	18.2 80°	18.5 79°	18.9 78°	19.3 77°	19.7 75°	20.5 73°	21.4 71°	22.3 69°	23.2 67°	24.1 66°	25.1 64°	26.0 63°	27.0 61°	28.0 60°	29.0 59°	34.1 55°	+14.0
+15.0	17.3 90°	17.6 88°	17.9 87°	18.2 85°	18.6 84°	19.0 82°	19.3 81°	19.7 80°	20.0 78°	20.4 77°	20.8 76°	21.6 74°	22.5 72°	23.4 70°	24.2 68°	25.2 67°	26.1 65°	27.0 64°	28.0 62°	29.0 61°	30.0 60°	35.1 55°	+15.0
+20.0	23.1 90°	23.5 89°	23.8 88°	24.0 87°	24.3 85°	24.7 84°	25.0 83°	25.4 82°	25.7 81°	26.1 80°	26.4 79°	27.2 77°	28.0 76°	28.8 74°	29.7 72°	30.6 71°	31.4 70°	32.3 68°	33.2 67°	34.1 65°	35.1 65°	40.0 60°	+20.0
	0.0	+0.5	+1.0	+1.5	+2.0	+2.5	+3.0	+3.5	+4.0	+4.5	+5.0	+6.0	+7.0	+8.0	+9.0	+10.0	+11.0	+12.0	+13.0	+14.0	+15.0	+20.0	

LEAD I

axes have been published by Wilson and collaborators,[2] Bayley,[8] Ashman and associates,[3–7] and Zuckermann.[10] The normal values cited by these authors have been obtained on relatively few patients and differ somewhat from each other. Certainly further study is necessary before final values can be established. A tentative list of normal values for directions of the axes of $\hat{A}_P$, $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ are modified from Zuckermann[10] (table 5). The magnitude of the P wave as determined from areas in normal children, between 3 months and 10 years of age, averages 1.6 units and varies between 0.8 and 3.4.[11] The magnitude of the mean electric axis of the QRS complex for men and women[10] averages 6.3 with a range of 3.5 to 12 units. The mean for males is 6.7 and for females 5.9.[4] The magnitude of the ventricular gradient averages 13 and varies from 2.5 to 23 units.[4] Certain relationships

TABLE 2.—*Magnitude and Direction of Electric Axis when Lead I Is Positive and Lead III Is Negative*

LEAD I

LEAD III	0.0	+0.5	+1.0	+1.5	+2.0	+2.5	+3.0	+3.5	+4.0	+4.5	+5.0	+6.0	+7.0	+8.0	+9.0	+10.0	+11.0	+12.0	+13.0	+14.0	+15.0	+20.0
0.0		.6 30°	1.2 30°	1.7 30°	2.3 30°	2.9 30°	3.5 30°	4.0 30°	4.6 30°	5.2 30°	5.8 30°	6.9 30°	8.1 30°	9.2 30°	10.4 30°	11.5 30°	12.7 30°	13.9 30°	15.0 30°	16.2 30°	17.3 30°	23.1 30°
-0.5	.6 -90°	.6 -30°	1.0 0°	1.5 11°	2.1 16°	2.6 19°	3.2 21°	3.8 22°	4.4 23°	4.9 24°	5.5 25°	6.7 26°	7.8 26°	9.0 27°	10.1 27°	11.3 27°	12.5 28°	13.6 28°	14.7 28°	15.9 28°	17.0 28°	22.9 29°
-1.0	1.2 -90°	1.0 -60°	1.2 -30°	1.5 -11°	2.0 0°	2.5 7°	3.1 11°	3.6 14°	4.2 16°	4.7 18°	5.3 19°	6.4 21°	7.6 22°	8.7 23°	9.9 24°	11.1 25°	12.2 25°	13.3 26°	14.5 26°	15.6 26°	16.7 27°	22.5 27°
-1.5	1.7 -90°	1.5 -71°	1.5 -49°	1.7 -30°	2.1 -16°	2.5 -7°	3.0 0°	3.5 5°	4.0 7°	4.6 11°	5.1 13°	6.3 16°	7.4 18°	8.5 20°	9.7 21°	10.8 22°	11.9 23°	13.1 23°	14.2 24°	15.4 24°	16.6 25°	22.3 26°
-2.0	2.3 -90°	2.1 -76°	2.0 -60°	2.1 -44°	2.3 -30°	2.6 -19°	3.1 -11°	3.5 -5°	4.0 0°	4.5 4°	5.0 7°	6.1 11°	7.2 14°	8.3 16°	9.5 18°	10.6 19°	11.7 20°	12.9 21°	14.0 22°	15.1 22°	16.3 23°	22.1 25°
-2.5	2.9 -90°	2.6 -79°	2.5 -67°	2.5 -53°	2.6 -41°	2.9 -30°	3.2 -21°	3.6 -14°	4.0 -8°	4.5 -4°	5.0 0°	6.0 6°	7.1 9°	8.2 12°	9.3 14°	10.4 16°	11.5 17°	12.7 19°	13.8 20°	14.9 20°	16.1 21°	21.8 23°
-3.0	3.5 -90°	3.2 -81°	3.1 -71°	3.0 -60°	3.1 -49°	3.2 -39°	3.5 -30°	3.8 -22°	4.2 -16°	4.6 -11°	5.0 -7°	6.0 0°	7.0 5°	8.1 8°	9.2 11°	10.3 13°	11.4 15°	12.5 16°	13.6 17°	14.7 18°	15.9 19°	21.6 22°
-3.5	4.0 -90°	3.8 -82°	3.6 -74°	3.5 -65°	3.5 -55°	3.6 -46°	3.8 -38°	4.0 -30°	4.4 -23°	4.7 -18°	5.1 -13°	6.0 -6°	7.0 0°	8.0 4°	9.1 7°	10.2 10°	11.3 12°	12.4 14°	13.5 15°	14.6 16°	15.7 17°	21.4 21°
-4.0	4.6 -90°	4.4 -83°	4.2 -76°	4.0 -68°	4.0 -60°	4.0 -52°	4.2 -44°	4.4 -37°	4.6 -30°	4.9 -24°	5.3 -19°	6.1 -11°	7.0 -5°	8.0 0°	9.0 4°	10.1 7°	11.1 9°	12.2 11°	13.3 13°	14.4 14°	15.5 15°	21.2 19°
-4.5	5.2 -90°	4.9 -84°	4.7 -78°	4.6 -71°	4.5 -64°	4.5 -56°	4.6 -49°	4.7 -42°	4.8 -36°	5.2 -30°	5.5 -25°	6.2 -16°	7.1 -9°	8.0 -4°	9.0 0°	10.0 3°	11.1 6°	12.1 8°	13.2 10°	14.3 12°	15.4 13°	21.0 18°
-5.0	5.8 -90°	5.5 -85°	5.3 -79°	5.1 -73°	5.0 -67°	5.0 -60°	5.0 -53°	5.1 -47°	5.3 -41°	5.5 -35°	5.8 -30°	6.4 -21°	7.2 -14°	8.1 -8°	9.0 -4°	10.0 0°	11.0 3°	12.1 6°	13.1 6°	14.2 9°	15.3 11°	20.8 16°
-6.0	6.9 -90°	6.7 -86°	6.4 -81°	6.3 -76°	6.1 -71°	6.0 -66°	6.0 -60°	6.0 -54°	6.1 -49°	6.2 -44°	6.4 -39°	6.9 -30°	7.6 -22°	8.3 -16°	9.2 -11°	10.1 -7°	11.0 -3°	12.0 0°	13.0 3°	14.0 5°	15.1 7°	20.5 13°
-7.0	8.1 -90°	7.8 -86°	7.6 -82°	7.4 -78°	7.2 -74°	7.1 -69°	7.0 -65°	7.0 -60°	7.0 -55°	7.1 -51°	7.2 -46°	7.6 -38°	8.1 -30°	8.7 -23°	9.5 -18°	10.3 -13°	11.1 -9°	12.1 -6°	13.0 -3°	14.0 0°	15.0 2°	20.3 10°
-8.0	9.2 -90°	9.0 -87°	8.7 -83°	8.5 -80°	8.3 -76°	8.2 -72°	8.1 -68°	8.0 -64°	8.0 -60°	8.0 -56°	8.1 -52°	8.3 -44°	8.7 -37°	9.2 -30°	9.9 -24°	10.6 -19°	11.4 -15°	12.2 -11°	13.1 -8°	14.0 -5°	15.0 -2°	20.1 7°
-9.0	10.4 -90°	10.1 -87°	9.9 -84°	9.7 -81°	9.5 -78°	9.3 -74°	9.2 -71°	9.1 -67°	9.0 -64°	9.0 -60°	9.0 -56°	9.2 -49°	9.5 -42°	9.9 -36°	10.4 -30°	11.0 -25°	11.7 -20°	12.5 -15°	13.3 -13°	14.2 -9°	15.1 -7°	20.0 3°
-10.0	11.5 -90°	11.3 -87°	11.1 -85°	10.8 -82°	10.6 -79°	10.4 -76°	10.3 -73°	10.2 -70°	10.1 -67°	10.0 -63°	10.0 -60°	10.1 -53°	10.3 -47°	10.6 -41°	11.0 -35°	11.5 -30°	12.2 -25°	12.9 -21°	13.6 -17°	14.4 -14°	15.3 -11°	20.0 0°
-11.0	12.7 -90°	12.5 -88°	12.2 -85°	11.9 -83°	11.7 -80°	11.5 -77°	11.4 -75°	11.3 -72°	11.1 -69°	11.1 -66°	11.0 -63°	11.0 -57°	11.1 -51°	11.4 -45°	11.7 -40°	12.2 -35°	12.7 -30°	13.3 -26°	14.0 -22°	14.7 -18°	15.5 -15°	20.0 -3°
-12.0	13.9 -90°	13.6 -88°	13.3 -86°	13.1 -83°	12.9 -81°	12.7 -79°	12.5 -76°	12.4 -74°	12.2 -71°	12.1 -68°	12.1 -66°	12.0 -60°	12.1 -54°	12.2 -49°	12.5 -44°	12.9 -39°	13.3 -34°	13.9 -30°	14.5 -26°	15.1 -22°	15.9 -19°	20.1 -7°
-13.0	15.0 -90°	14.7 -88°	14.5 -86°	14.2 -84°	14.0 -82°	13.8 -80°	13.6 -77°	13.5 -75°	13.3 -73°	13.2 -70°	13.1 -68°	13.0 -63°	13.0 -57°	13.1 -52°	13.3 -47°	13.6 -43°	14.0 -38°	14.5 -34°	15.0 -30°	15.6 -26°	16.3 -23°	20.3 -10°
-14.0	16.2 -90°	15.9 -88°	15.6 -86°	15.4 -84°	15.1 -82°	14.9 -80°	14.7 -78°	14.6 -76°	14.4 -74°	14.3 -72°	14.2 -69°	14.0 -65°	14.0 -60°	14.0 -55°	14.2 -51°	14.4 -46°	14.7 -42°	15.1 -38°	15.6 -34°	16.2 -30°	16.8 -27°	20.5 -13°
-15.0	17.3 -90°	17.0 -88°	16.7 -87°	16.6 -85°	16.3 -83°	16.1 -81°	15.9 -79°	15.7 -77°	15.5 -75°	15.4 -73°	15.3 -71°	15.1 -67°	15.0 -62°	15.0 -58°	15.1 -53°	15.3 -49°	15.5 -45°	15.9 -41°	16.3 -37°	16.8 -33°	17.3 -30°	20.8 -16°
-20.0	23.1 -90°	22.9 -89°	22.5 -87°	22.3 -86°	22.1 -85°	21.8 -83°	21.6 -82°	21.4 -81°	21.2 -79°	21.0 -78°	20.8 -76°	20.5 -73°	20.3 -70°	20.1 -67°	20.0 -63°	20.0 -60°	20.0 -57°	20.1 -53°	20.3 -50°	20.5 -47°	20.8 -44°	23.1 -30°

LEAD I

between these axes are known at the present time. Normally, the mean electric axis of the QRS complex is approximately one-half of the magnitude of the gradient with considerable variation. The gradient ordinarily lies less than 20 degrees to the right or left of the anatomic axis of the heart.[12] The mean electric axis of the QRS ordinarily lies not more than 35 degrees to the left or 25 degrees to the right of the gradient.[12]

The use of these axes, particularly the ventricular gradient, is sometimes important in revealing abnormalities in the electrocardiogram, in determining the degree of digitalization, in showing types of rotational disturbances, in detecting areas of myocardial ischemia, injury, or death, and in revealing the presence of auricular or ventricular strain. In general, the ventricular gradient, when abnormal because of local ventricular ischemia, has a direc-

TABLE 3.—*Magnitude and Direction of Electric Axis when Leads I and III Are Negative*

LEAD III \ LEAD I	0.0	-0.5	-1.0	-1.5	-2.0	-2.5	-3.0	-3.5	-4.0	-4.5	-5.0	-6.0	-7.0	-8.0	-9.0	-10.0	-11.0	-12.0	-13.0	-14.0	-15.0	-20.0
0.0		.6 -150°	1.2 -150°	1.7 -150°	2.3 -150°	2.9 -150°	3.5 -150°	4.0 -150°	4.6 -150°	5.2 -150°	5.8 -150°	6.9 -150°	8.1 -150°	9.2 -150°	10.4 -150°	11.5 -150°	12.7 -150°	13.9 -150°	15.0 -150°	16.2 -150°	17.3 -150°	23.1 -150°
-0.5	.6 -90°	1.0 -120°	1.5 -131°	2.1 -136°	2.6 -139°	3.2 -141°	3.8 -142°	4.4 -143°	4.9 -144°	5.5 -145°	6.1 -145°	7.2 -146°	8.4 -147°	9.6 -147°	10.7 -147°	11.9 -148°	13.0 -148°	14.1 -148°	15.3 -148°	16.4 -148°	17.6 -148°	23.5 -149°
-1.0	1.2 -90°	1.5 -109°	2.0 -120°	2.5 -127°	3.1 -131°	3.6 -134°	4.2 -136°	4.7 -138°	5.3 -139°	5.9 -140°	6.4 -141°	7.6 -142°	8.7 -143°	9.9 -144°	11.0 -145°	12.2 -145°	13.3 -146°	14.5 -146°	15.6 -146°	16.8 -147°	17.9 -147°	23.8 -148°
-1.5	1.7 -90°	2.1 -104°	2.5 -113°	3.0 -120°	3.5 -125°	4.0 -128°	4.6 -131°	5.1 -133°	5.7 -135°	6.3 -136°	6.8 -137°	7.9 -139°	9.1 -141°	10.2 -142°	11.4 -142°	12.5 -143°	13.7 -144°	14.8 -144°	16.0 -144°	17.1 -145°	18.2 -145°	24.0 -147°
-2.0	2.3 -90°	2.6 -101°	3.1 -109°	3.5 -115°	4.0 -120°	4.5 -124°	5.0 -127°	5.6 -129°	6.1 -131°	6.7 -133°	7.2 -134°	8.3 -136°	9.5 -138°	10.6 -139°	11.7 -140°	12.9 -141°	14.0 -142°	15.1 -142°	16.3 -143°	17.4 -143°	18.6 -144°	24.3 -145°
-2.5	2.9 -90°	3.2 -99°	3.6 -106°	4.0 -112°	4.5 -116°	5.0 -120°	5.5 -123°	6.0 -126°	6.6 -128°	7.1 -129°	7.6 -131°	8.7 -133°	9.9 -135°	11.0 -137°	12.1 -138°	13.2 -139°	14.4 -140°	15.6 -141°	16.7 -141°	17.8 -142°	19.0 -142°	24.7 -144°
-3.0	3.5 -90°	3.8 -98°	4.2 -104°	4.6 -109°	5.0 -113°	5.5 -117°	6.0 -120°	6.5 -123°	7.0 -125°	7.5 -127°	8.1 -128°	9.2 -131°	10.3 -133°	11.4 -135°	12.5 -136°	13.6 -137°	14.7 -138°	15.9 -139°	17.1 -140°	18.2 -141°	19.3 -141°	25.0 -143°
-3.5	4.0 -90°	4.4 -97°	4.7 -102°	5.1 -107°	5.6 -111°	6.0 -114°	6.5 -117°	7.0 -120°	7.5 -122°	8.0 -124°	8.6 -124°	9.6 -129°	10.7 -131°	11.8 -133°	12.9 -134°	14.0 -136°	15.2 -137°	16.3 -138°	17.4 -138°	18.5 -139°	19.7 -140°	25.4 -142°
-4.0	4.6 -90°	4.9 -96°	5.3 -101°	5.7 -105°	6.1 -109°	6.6 -112°	7.0 -115°	7.5 -118°	8.0 -120°	8.5 -122°	9.0 -124°	10.1 -127°	11.1 -129°	12.2 -131°	13.3 -133°	14.4 -134°	15.5 -135°	16.7 -136°	17.8 -137°	18.9 -138°	20.0 -138°	25.7 -141°
-4.5	5.2 -90°	5.5 -95°	5.9 -100°	6.3 -104°	6.7 -107°	7.1 -111°	7.5 -113°	8.0 -116°	8.5 -118°	9.0 -120°	9.5 -122°	10.5 -125°	11.6 -127°	12.7 -129°	13.7 -131°	14.8 -132°	16.0 -133°	17.1 -135°	18.2 -136°	19.3 -137°	20.4 -137°	26.1 -140°
-5.0	5.8 -90°	6.1 -95°	6.4 -99°	6.8 -103°	7.2 -106°	7.6 -109°	8.1 -112°	8.6 -114°	9.0 -116°	9.5 -118°	10.0 -120°	11.0 -123°	12.1 -125°	13.1 -128°	14.2 -129°	15.3 -131°	16.4 -132°	17.5 -133°	18.6 -134°	19.7 -135°	20.8 -136°	26.4 -139°
-6.0	6.9 -90°	7.2 -94°	7.6 -98°	7.9 -101°	8.3 -104°	8.7 -107°	9.2 -109°	9.6 -111°	10.1 -113°	10.5 -115°	11.0 -117°	12.0 -120°	13.0 -123°	14.0 -125°	15.1 -127°	16.2 -128°	17.2 -130°	18.3 -131°	19.4 -132°	20.5 -133°	21.6 -134°	27.2 -137°
-7.0	8.1 -90°	8.4 -93°	8.7 -97°	9.1 -99°	9.5 -102°	9.9 -105°	10.3 -107°	10.7 -109°	11.1 -111°	11.6 -113°	12.1 -115°	13.0 -117°	14.0 -120°	15.0 -122°	16.0 -124°	17.1 -126°	18.2 -127°	19.2 -129°	20.3 -130°	21.4 -131°	22.5 -132°	28.0 -136°
-8.0	9.2 -90°	9.6 -93°	9.9 -96°	10.2 -98°	10.6 -101°	11.0 -103°	11.4 -105°	11.8 -107°	12.2 -109°	12.7 -111°	13.1 -112°	14.0 -115°	15.0 -118°	16.0 -120°	17.0 -122°	18.0 -124°	19.1 -125°	20.1 -127°	21.2 -128°	22.3 -129°	23.4 -130°	28.8 -134°
-9.0	10.4 -90°	10.7 -93°	11.0 -95°	11.4 -98°	11.7 -100°	12.1 -102°	12.5 -104°	12.9 -106°	13.3 -107°	13.7 -109°	14.2 -111°	15.1 -113°	16.0 -116°	17.0 -118°	18.0 -120°	19.0 -122°	20.0 -123°	21.1 -125°	22.1 -126°	23.2 -127°	24.2 -128°	29.7 -132°
-10.0	11.5 -90°	11.9 -92°	12.2 -95°	12.5 -97°	12.9 -99°	13.2 -101°	13.6 -103°	14.0 -104°	14.4 -106°	14.8 -108°	15.3 -109°	16.2 -112°	17.1 -114°	18.0 -116°	19.0 -118°	20.0 -120°	21.0 -122°	22.0 -123°	23.1 -124°	24.1 -126°	25.2 -127°	30.6 -131°
-11.0	12.7 -90°	13.0 -92°	13.3 -94°	13.7 -96°	14.0 -98°	14.4 -100°	14.7 -102°	15.1 -103°	15.5 -105°	16.0 -107°	16.4 -108°	17.2 -110°	18.2 -113°	19.1 -115°	20.0 -117°	21.0 -118°	22.0 -120°	23.0 -121°	24.0 -123°	25.1 -124°	26.1 -125°	31.4 -130°
-12.0	13.9 -90°	14.1 -92°	14.5 -94°	14.8 -96°	15.1 -98°	15.6 -99°	15.9 -101°	16.3 -102°	16.7 -104°	17.1 -105°	17.5 -107°	18.3 -109°	19.2 -111°	20.1 -113	21.1 -115°	22.0 -117°	23.0 -119°	24.0 -120°	25.0 -121°	26.0 -123°	27.0 -124°	32.3 -128°
-13.0	15.0 -90°	15.3 -92°	15.6 -94°	16.0 -96°	16.3 -97°	16.7 -99°	17.1 -100°	17.4 -102°	17.8 -103°	18.2 -104°	18.6 -106°	19.4 -108°	20.3 -110°	21.2 -112°	22.1 -114°	23.1 -116°	24.0 -117°	25.0 -119°	26.0 -120°	27.0 -121°	28.0 -122°	33.2 -127°
-14.0	16.2 -90°	16.4 -92°	16.8 -93°	17.1 -95°	17.4 -97°	17.8 -98°	18.2 -100°	18.5 -101°	18.9 -102°	19.3 -103°	19.7 -105°	20.5 -107°	21.4 -109°	22.3 -111°	23.2 -113°	24.1 -114°	25.1 -116°	26.0 -117°	27.0 -119°	28.0 -120°	29.0 -121°	34.1 -125°
-15.0	17.3 -90°	17.6 -92°	17.9 -93°	18.2 -95°	18.6 -96°	19.0 -98°	19.3 -99°	19.7 -100°	20.0 -102°	20.4 -103°	20.8 -104°	21.6 -106°	22.5 -108°	23.4 -110°	24.2 -112°	25.2 -113°	26.1 -115°	27.0 -116°	28.0 -118°	29.0 -119°	30.0 -120°	35.1 -125°
-20.0	23.1 -90°	23.5 -91°	23.8 -92°	24.0 -93°	24.3 -95°	24.7 -96°	25.0 -97°	25.4 -98°	25.7 -99°	26.1 -100°	26.4 -101°	27.2 -103°	28.0 -104°	28.8 -106°	29.7 -108°	30.6 -109°	31.4 -110°	32.3 -112°	33.2 -113°	34.1 -115°	35.1 -115°	40.0 -120°

tion which tends toward that of a line drawn from the ischemic region (where the average duration of the excited state is greatest) to the centroid of the involved ventricle. With moderate grades of apical ischemia the direction of the gradient is toward the ischemic region but the magnitude of the gradient is reduced. The magnitude of the gradient is large in ischemia at the base of the heart and small with ischemia at the apex of the heart. With left ventricular strain there is often growth and rotation of the mean electric axis of the QRS complex to the left with respect to the anatomic axis. With right ventricular strain there is often growth and rotation of the mean electric axis of the QRS complex to the right with respect to the anatomic axis of the heart. These rotational effects with hypertrophy are variable, however, and depend in large part upon the electrocardiographic position of the heart in the chest. For example, with left ventricular hypertrophy, $\hat{A}_{QRS}$ may

TABLE 4.—*Magnitude and Direction of Electric Axis when Lead I Is Negative and Lead III Positive*

LEAD I

LEAD III	0.0	-0.5	-1.0	-1.5	-2.0	-2.5	-3.0	-3.5	-4.0	-4.5	-5.0	-6.0	-7.0	-8.0	-9.0	-10.0	-11.0	-12.0	-13.0	-14.0	-15.0	-20.0
0.0		.6 -150°	1.2 -150°	1.7 -150°	2.3 -150°	2.9 -150°	3.5 -150°	4.0 -150°	4.6 -150°	5.2 -150°	5.8 -150°	6.9 -150°	8.1 -150°	9.2 -150°	10.4 -150°	11.5 -150°	12.7 -150°	13.9 -150°	15.0 -150°	16.2 -150°	17.3 -150°	23.1 -150°
+0.5	.6 90°	.6 150°	1.0 180°	1.5 -169°	2.1 -164°	2.6 -161°	3.2 -159°	3.8 -158°	4.4 -157°	4.9 -156°	5.5 -155°	6.7 -154°	7.8 -154°	9.0 -153°	10.1 -153°	11.3 -153°	12.5 -152°	13.6 -152°	14.7 -152°	15.9 -152°	17.0 -152°	22.9 -151°
+1.0	1.2 90°	1.0 120°	1.2 150°	1.5 169°	2.0 180°	2.5 -173°	3.1 -169°	3.6 -166°	4.2 -164°	4.7 -162°	5.3 -161°	6.4 -159°	7.6 -158°	8.7 -157°	9.9 -156°	11.1 -155°	12.2 -155°	13.3 -154°	14.5 -154°	15.6 -154°	16.7 -153°	22.5 -153°
+1.5	1.7 90°	1.5 109°	1.5 131°	1.7 150°	2.1 164°	2.5 173°	3.0 180°	3.5 -175°	4.0 -172°	4.6 -169°	5.1 -167°	6.3 -164°	7.4 -162°	8.5 -160°	9.7 -159°	10.8 -158°	11.9 -157°	13.1 -157°	14.2 -156°	15.4 -156°	16.6 -155°	22.3 -154°
+2.0	2.3 90°	2.1 104°	2.0 120°	2.1 136°	2.3 150°	2.6 161°	3.1 169°	3.5 175°	4.0 180°	4.5 -176°	5.0 -173°	6.1 -169°	7.2 -166°	8.3 -164°	9.5 -162°	10.6 -161°	11.7 -160°	12.9 -159°	14.0 -158°	15.1 -158°	16.3 -157°	22.1 -155°
+2.5	2.9 90°	2.6 101°	2.5 113°	2.5 127°	2.6 139°	2.9 150°	3.2 159°	3.6 166°	4.0 172°	4.5 176°	5.0 180°	6.0 -174°	7.1 -171°	8.2 -168°	9.3 -166°	10.4 -164°	11.5 -163°	12.7 -161°	13.8 -160°	14.9 -160°	16.1 -159°	21.8 -157°
+3.0	3.5 90°	3.2 99°	3.1 109°	3.0 120°	3.1 131°	3.2 141°	3.5 150°	3.8 158°	4.2 164°	4.6 169°	5.0 173°	6.0 180°	7.0 -175°	8.1 -172°	9.2 -169°	10.3 -167°	11.4 -165°	12.5 -164°	13.6 -163°	14.7 -162°	15.9 -161°	21.6 -158°
+3.5	4.0 90°	3.8 98°	3.6 106°	3.5 115°	3.5 125°	3.6 134°	3.8 142°	4.0 150°	4.4 157°	4.7 162°	5.1 167°	6.0 174°	7.0 180°	8.0 -176°	9.1 -173°	10.2 -170°	11.3 -168°	12.4 -166°	13.5 -165°	14.6 -164°	15.7 -163°	21.4 -159°
+4.0	4.6 90°	4.4 97°	4.2 104°	4.0 112°	4.0 120°	4.0 128°	4.2 136°	4.4 143°	4.6 150°	4.9 156°	5.3 161°	6.1 169°	7.0 175°	8.0 180°	9.0 -176°	10.1 -173°	11.1 -171°	12.2 -169°	13.3 -167°	14.4 -166°	15.5 -165°	21.2 -161°
+4.5	5.2 90°	4.9 96°	4.7 102°	4.6 109°	4.5 116°	4.5 124°	4.6 131°	4.7 138°	4.9 144°	5.2 150°	5.5 155°	6.2 164°	7.1 171°	8.0 176°	9.0 180°	10.0 -177°	11.1 -174°	12.1 -172°	13.2 -170°	14.3 -168°	15.4 -167°	21.0 -162°
+5.0	5.8 90°	5.5 95°	5.3 101°	5.1 107°	5.0 113°	5.0 120°	5.0 127°	5.1 133°	5.3 139°	5.5 145°	5.8 150°	6.4 159°	7.2 166°	8.1 172°	9.0 176°	10.0 180°	11.0 -177°	12.1 -174°	13.1 -172°	14.2 -171°	15.3 -169°	20.8 -164°
+6.0	6.9 90°	6.7 94°	6.4 99°	6.3 104°	6.1 109°	6.0 114°	6.0 120°	6.0 126°	6.1 131°	6.2 136°	6.4 141°	6.9 150°	7.6 158°	8.3 164°	9.2 169°	10.1 173°	11.0 177°	12.0 180°	13.0 -177°	14.0 -175°	15.1 -173°	20.5 -167°
+7.0	8.1 90°	7.8 94°	7.6 98°	7.4 102°	7.2 106°	7.1 111°	7.0 115°	7.0 120°	7.0 125°	7.1 129°	7.2 134°	7.6 142°	8.1 150°	8.7 157°	9.5 162°	10.3 167°	11.1 171°	12.1 174°	13.0 177°	14.0 180°	15.0 -178°	20.3 -170°
+8.0	9.2 90°	9.0 93°	8.7 97°	8.5 100°	8.3 104°	8.2 108°	8.1 112°	8.0 116°	8.0 120°	8.0 124°	8.1 128°	8.3 136°	8.7 143°	9.2 150°	9.9 156°	10.6 161°	11.4 165°	12.2 169°	13.1 172°	14.0 175°	15.0 178°	20.1 -173°
+9.0	10.4 90°	10.1 93°	9.9 96°	9.7 99°	9.5 102°	9.3 106°	9.2 109°	9.1 113°	9.0 116°	9.0 120°	9.0 124°	9.2 131°	9.5 138°	9.9 144°	10.4 150°	11.0 155°	11.7 160°	12.5 164°	13.3 167°	14.2 171°	15.1 173°	20.0 -177°
+10.0	11.5 90°	11.3 93°	11.1 95°	10.8 98°	10.6 101°	10.4 104°	10.3 107°	10.2 110°	10.1 113°	10.0 117°	10.0 120°	10.1 127°	10.3 133°	10.6 139°	11.0 145°	11.5 150°	12.2 155°	12.9 159°	13.6 163°	14.4 166°	15.3 169°	20.0 180°
+11.0	12.7 90°	12.5 92°	12.2 95°	11.9 97°	11.7 100°	11.5 103°	11.4 105°	11.3 108°	11.1 111°	11.1 114°	11.0 117°	11.0 123°	11.1 129°	11.4 135°	11.7 140°	12.2 145°	12.7 150°	13.3 154°	14.0 158°	14.7 162°	15.5 165°	20.0 177°
+12.0	13.9 90°	13.6 92°	13.3 94°	13.1 97°	12.9 99°	12.7 101°	12.5 104°	12.4 106°	12.2 109°	12.1 112°	12.1 114°	12.0 120°	12.1 126°	12.2 131°	12.5 136°	12.9 141°	13.3 146°	13.9 150°	14.5 154°	15.1 158°	15.9 161°	20.1 173°
+13.0	15.0 90°	14.7 92°	14.5 94°	14.2 96°	14.0 98°	13.8 100°	13.6 103°	13.5 105°	13.3 107°	13.2 110°	13.1 112°	13.0 117°	13.0 123°	13.1 128°	13.3 133°	13.6 137°	14.0 142°	14.5 146°	15.0 150°	15.6 154°	16.3 157°	20.3 170°
+14.0	16.2 90°	15.9 92°	15.6 94°	15.4 96°	15.1 98°	14.9 100°	14.7 102°	14.6 104°	14.4 106°	14.3 108°	14.2 111°	14.0 115°	14.0 120°	14.0 125°	14.2 129°	14.4 134°	14.7 138°	15.1 142°	15.6 146°	16.2 150°	16.8 153°	20.5 167°
+15.0	17.3 90°	17.0 92°	16.7 93°	16.6 95°	16.3 97°	16.1 99°	15.9 101°	15.7 103°	15.5 105°	15.4 107°	15.3 109°	15.1 113°	15.0 118°	15.0 122°	15.1 127°	15.3 131°	15.5 135°	15.9 139°	16.3 143°	16.8 147°	17.3 150°	20.8 164°
+20.0	23.1 90°	22.9 91°	22.5 93°	22.3 94°	22.1 95°	21.8 97°	21.6 98°	21.4 99°	21.2 101°	21.0 102°	20.8 104°	20.5 107°	20.3 110°	20.1 113°	20.0 117°	20.0 120°	20.0 123°	20.1 127°	20.3 130°	20.5 133°	20.8 136°	23.1 150°

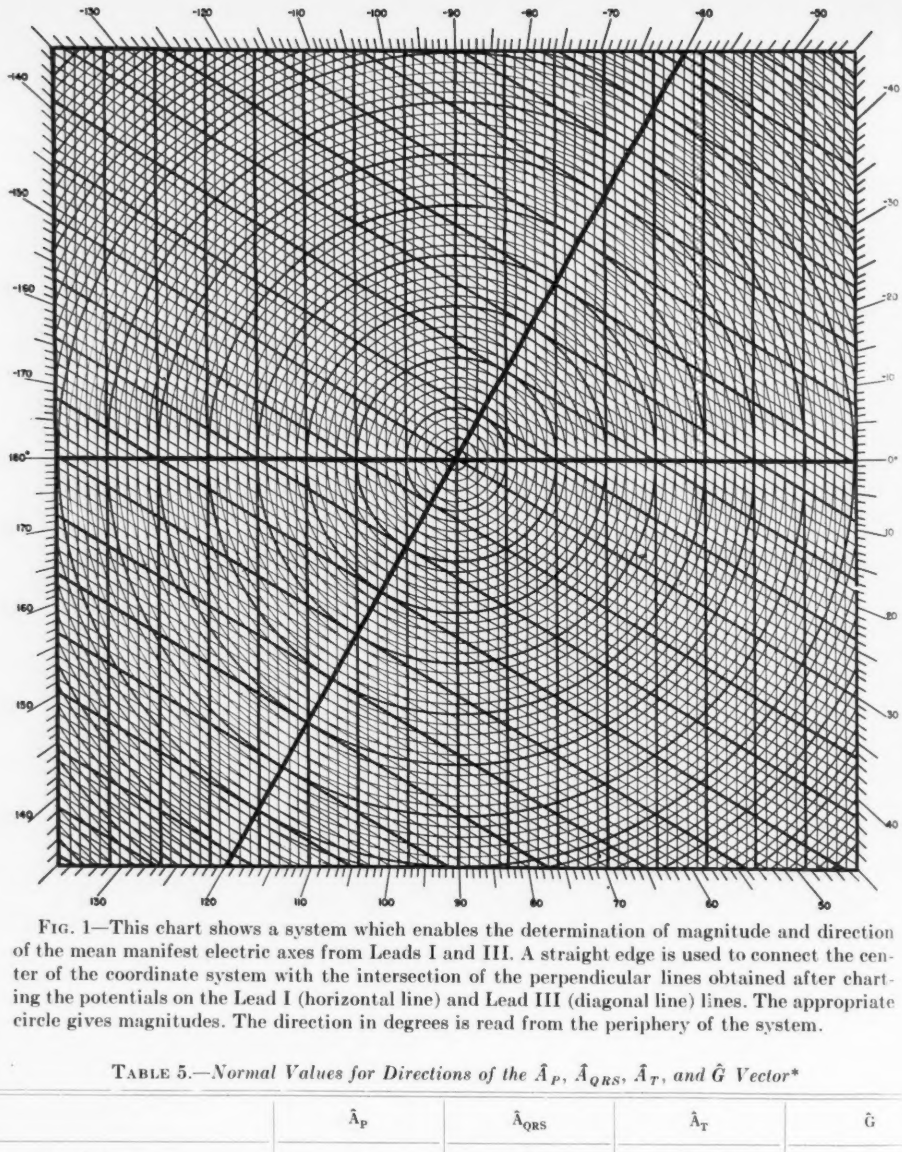

FIG. 1—This chart shows a system which enables the determination of magnitude and direction of the mean manifest electric axes from Leads I and III. A straight edge is used to connect the center of the coordinate system with the intersection of the perpendicular lines obtained after charting the potentials on the Lead I (horizontal line) and Lead III (diagonal line) lines. The appropriate circle gives magnitudes. The direction in degrees is read from the periphery of the system.

TABLE 5.—*Normal Values for Directions of the $\hat{A}_P$, $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ Vector**

	$\hat{A}_P$	$\hat{A}_{QRS}$	$\hat{A}_T$	$\hat{G}$
1. Normal adult	64°	58° (0–90°)	38° (0 to 83°)	−17 to 86°
2. Normal adult with tachycardia				−25 to 86°
3. Obesity		−30° to 0		
4. Normal child: newborn		130°		
1st 3 mos.		90°		
1–5 years	46° (30 to 79°)†	52°		
5. Right auricular strain	60 to 90°			
6. Left auricular strain	0 to +55°			
7. Right ventricular strain		+90 to −90°	−90 to +90°	wide range
8. Left ventricular strain		−60 to 60°	−4 to −144°	−57 to 12[illegible]
9. Right BBB		120 to −60°	−60° to 60°	−60 to 90
10. Left BBB		−60° to 0°	60 to −120°	−60 to 60
11. Subacute posterior infarct			−90° to 0°	−90° to 0
12. Subacute anterior infarct			90 to 180°	60 to 180

* All measurements are read in a clockwise direction. All values are derived from areas of the electrocardiogram.

† Reference 11.

rotate to the left, not at all, or to the right depending upon whether the electrocardiographic position of the heart is horizontal, intermediate, or vertical.

Summary

Tables and a chart for the estimation of the magnitude and direction of the electric axes of the electrocardiogram are presented. The axes of the P wave, QRS complex, T wave, RS-T segment, and ventricular gradient may be determined, using either amplitudes in millimeters or millivolts or areas in units or microvolt seconds. Certain normal values for magnitude and direction of these axes are presented.

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Electrocardiographic Changes in Pulmonary Collapse Therapy

II. Thoracoplasty and Phrenemphraxis

By Charles Silverberg, M.D. and David Feldman, M.D.

The effect of thoracoplasty and phrenemphraxis upon the electrocardiographic pattern of tuberculous patients was studied. Alteration in the size of QRS complexes resulted in variable changes in the mean electrical axis. Some alterations in T waves occurred in all leads, occasionally resulting in inversion of the T waves in Leads CF_2, CF_4 and/or CF_5. There was no pattern characteristic of any of the collapse procedures studied.

IN A PREVIOUS article[1] it was pointed out that in a tuberculosis sanatorium, as in any other medical institution, electrocardiograms are often made for diagnostic reasons. Many of the patients will have been subjected to pulmonary collapse therapy, and it is important to be aware of any electrocardiographic changes which may be caused by this collapse therapy, lest such changes be attributed to myocardial disease. For this reason an electrocardiographic study was made in patients undergoing pulmonary collapse therapy.

Method

The method employed in this study has been described in our previous report, which dealt with findings in therapeutic pneumothorax.[1] Because of the removal of the ribs which constituted the landmarks for the placement of the precordial electrode in the C_4 and C_5 positions, difficulty arose in taking tracings on patients with left thoracoplasty. In such patients, position C_{4R} was determined, and this level was used in the placement of the electrode in the C_4 and C_5 positions on the left side. In patients with phrenic crush, diaphragmatic paralysis was verified fluoroscopically. All changes encountered in the post-collapse tracing were noted and tabulated, and are the basis for this report. A total of 35 cases was analyzed: 14 of left thoracoplasty, 9 of right thoracoplasty, 6 of left phrenemphraxis and 6 of right phrenemphraxis. These cases were consecutive and unselected.

Results and Discussion

A tabulation of the changes encountered in each case may be found in table 1. Figure 1 shows representative electrocardiograms from a patient undergoing each type of collapse procedure.

Everyone experienced in collapse therapy of pulmonary tuberculosis knows how regularly pulmonary collapse procedures are followed by shifts in the position of the heart. Positional changes of the heart have long been known to cause electrocardiographic alterations.[2] It is therefore to be expected that pulmonary collapse procedures will be followed by electrocardiographic changes. This work was undertaken for the purpose of studying these electrocardiographic changes in a group of patients and to try to determine whether the electrocardiographic changes would fall into any recognizable pattern which might be diagnostic of the particular collapse procedure and whether the changes were of a variety likely to be confused with those produced by myocardial disease.

Other investigators have noted changes in the electrocardiogram following thoracoplasty and diaphragmatic paralysis.[3–7] Most of their reports dealt with limb leads only, being written prior to the time of the widespread use of precordial leads. As was our experience, these investigators found a variety of nonspecific changes following the collapse procedure, such as alterations in the size of various parts of the QRS complex,[4–7] changes in the mean electrical axis of the QRS complex,[4, 7] and T-wave changes, especially in Lead III.[3–6]

In our cases of left and right thoracoplasty and left and right phrenemphraxis, electrocardiographic changes were frequent following the collapse procedure, but were often very

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slight in degree. The fact that many of the changes tabulated were so slight must be emphasized, because changes of the same order of magnitude (in the limb leads) may be seen at times in serial electrocardiograms in tuberculous individuals without collapse procedure.[7] Frequently there were changes in amplitude of various waves of the QRS complexes of the limb leads, leading to changes in the mean electrical axis of the QRS complex. Usually this change was slight, but in a few instances (Patients H and W) it was rather pronounced. In right thoracoplasty and right diaphragmatic paralysis the axis shift showed a tendency to be toward the right, in left diaphragmatic paralysis the shift tended to be toward the left, and in left thoracoplasty there was no predominance in axis shift toward either right or left. Others have observed less consistent changes in the electrical axis.[6, 7]

Changes in T waves in the limb leads were frequent but variable in direction, and usually of slight magnitude. There were a few patients who had a change in the direction of T_3. In two patients with left thoracoplasty a previously inverted T_3 became upright, and in two patients (one with left thoracoplasty and one with right phrenemphraxis) a previously upright T_3 became inverted.

In the chest leads, alterations of amplitude of various waves in the QRS complex were common, but usually not of a degree that could be considered significant. Similarly, minor alterations in T-wave amplitude were frequent in the precordial leads. In a few patients, however, precordial T-wave changes of significance were present following the collapse therapy. Thus, in two patients with left thoracoplasty and one with right thoracoplasty, a previously upright T-wave in Lead CF_2 became inverted; in one patient with left phrenic paralysis the T wave became inverted in both CF_4 and CF_5; in one patient with right phrenic paralysis, the T wave became inverted in CF_4.

Shifts of the anatomic position of the heart are encountered with regularity in pulmonary collapse procedures. The exact nature of the shift, however, is undoubtedly influenced by a variety of factors besides the extent and type of the collapse procedure used, e.g., adhesions between various intrathoracic structures, body habitus, and pulmonary consolidation or fibrosis. If the changes in the electrocardiogram are due to alterations in cardiac position, it is not surprising that so little regularity was present in the changes encountered. Dubrow[8] has described biochemical and histologic alterations in the myocardium of dogs subject to thoracoplasty, but in none of our thoracoplasty subjects or other patients was there any reason clinically to suspect any myocardial involvement. Furthermore, other investigators have been unable to find more degenerative changes in the hearts of thoracoplasty patients than in the hearts of other tuberculous patients.[7]

Summary and Conclusions

1. An electrocardiographic study was made on an unselected series of patients undergoing therapeutic thoracoplasty or phrenemphraxis for pulmonary tuberculosis. Electrocardiograms and chest roentgenograms were made prior to institution of the collapse procedure and after its completion. A total of 35 patients was so studied: 14 with left thoracoplasty, 9 with right thoracoplasty, 6 with left phrenemphraxis, and 6 with right phrenemphraxis. Electrocardiographic changes were tabulated and described.

2. Some alteration in the size of various waves in the QRS complexes in the limb and precordial leads was generally found, leading, in the case of the limb leads, to variable changes in the mean electrical axis of the QRS complex. In right thoracoplasty and right phrenic paralysis the axis tended to shift slightly toward the right, and in left phrenic paralysis, toward the left. In left thoracoplasty, slight shifts occurred in both directions with approximately equal frequency.

3. Minor alterations in T-wave amplitude in the limb and precordial leads were frequent. In some patients there was a change in direction of T_3. In a few patients the postcollapse electrocardiogram became abnormal because of inversion of the T wave in one or more of the precordial leads, CF_2, CF_4, and CF_5.

4. No pattern of changes was found which was characteristic of any of the collapse procedures investigated.

Table 1.—*Electrocardiographic Changes Produced by Pulmonary Collapse Procedure in Each Case*

Patient	Age and Sex	T.B. Diag.*	Collapse†	Heart Position‡	QRS Axis§	Changes in Limb Leads I and III		Changes in Precordial Leads CF_2, CF_4, and CF_5		Remarks
						QRS	T Waves	QRS	T Waves	
				(cm.)						
A. R. B.	40 M	F A III	LT		+73 +84	QRS_1 less upright; QRS_3 larger			Inverted in CF_2 (was upright); taller in CF_4 and CF_5	7 ribs removed. Base of heart displaced slightly to right
B. E. B.	29 M	F A III	LT		+83 +81	QRS_3 smaller	T_3 smaller	Smaller in CF_2, CF_4, CF_5	Taller in CF_2	8 ribs removed. P_1 smaller. No apparent change in heart position
C. E. G.	24 F	F A II	LT		+69 +81	QRS_1 smaller	T_1 smaller; T_3 less inverted	Larger and more upright in CF_4 and CF_5		7 ribs removed. No apparent change in heart position
D. R. D.	40 M	F A II	LT		+60 +38	QRS_1 larger and less notched	T_1 smaller; T_3 inverted (was upright)	Smaller and more upright in CF_5		7 ribs removed. Heart markedly displaced to right
E. V. N.	21 F	F A III	LT		+60 +68	QRS_1 smaller; QRS_3 larger and more upright	T_3 upright (was inverted)	Larger in CF_2; smaller and more upright in CF_4 and CF_5	Diphasic in CF_2 (was upright)	8 ribs removed. Illustrated. X-ray films not available
F. E. M.	22 F	F A III	LT		+93 +98	QRS_1 smaller	T_1 smaller; T_3 taller	More upright in CF_4 and CF_5	Smaller in all leads	4 ribs removed. Apex of heart markedly displaced to right
G. J. C.	22 M	F A II	LT		+75 +60	QRS_3 smaller and less upright		Larger in CF_5	Taller in CF_5	8 ribs removed. Heart slightly displaced to right
I. J. H.	33 M	F A II	LT		+55 −36	QRS_3 inverted (was upright)	T_1 taller		Smaller in all leads	5 ribs removed. X-ray films not available
I. M. W.	16 F	F A III	LT		+83 +94	QRS_1 less upright	T_3 more inverted	Larger and more upright in CF_4 and CF_5	Smaller in CF_4	7 ribs removed. No apparent change in heart position

Table 1—*continued*

Patient	Age and Sex	T.B. Diag.*	Collapse†	Heart Position‡ (cm.)	QRS Axis§	Changes in Limb Leads I and III: QRS	Changes in Limb Leads I and III: T Waves	Changes in Precordial Leads CF_2, CF_4, and CF_5: QRS	Changes in Precordial Leads CF_2, CF_4, and CF_5: T Waves	Remarks
J. M. M	24 F	F A II	LT		+40 +38		T_1 taller; T_3 inverted (was upright)	Larger in CF_5	Inverted in CF_2 (was upright); taller in CF_4 and CF_5	6 ribs removed. Heart moderately displaced to left
K. E. H.	42 M	F A II	LT		+55 +38	QRS_3 smaller and less upright	T_1 taller; T_3 smaller			7 ribs removed. Heart slightly displaced to right
L. J. R.	29 F	F A III	LT		+75 +67			More upright in CF_4 and CF_5	Smaller in all leads	7 ribs removed. Heart moderately displaced to right
M. J. B.	54 M	F A II	LT		+75 +80			More upright in all leads	Taller in CF_4 and CF_5	6 ribs removed. No apparent change in heart position
N. M. L.	40 F	M A II	LT		+50 +45	QRS_1 smaller; QRS_3 less upright	T_1 smaller	Larger in CF_5	Taller in CF_5	7 ribs removed. No apparent change in heart position
O. J. S.	32 M		RT		+43 +10	QRS_3 smaller, more inverted		Larger in CF_4 and CF_5	Taller in CF_4 and CF_5	7 ribs removed. Heart slightly displaced to left
P. F. E.	23 F	F A II	RT		+17 +30	QRS_3 less inverted		Smaller in CF_2; less inverted in CF_4 and CF_5	Inverted in CF_2 (was upright)	5 ribs removed. No apparent change in heart position
Q. D. A.	48 M	F A II	RT		+70 +73		T_1 and T_3 smaller	Larger in CF_5	Taller in CF_2 and CF_4	6 ribs removed. Illustrated. Heart moderately displaced to left
R. R. S	24 M	F A III	RT		+137 +142			Larger and less inverted in CF_5	Taller in CF_4	7 ribs removed. Heart moderately displaced to left
S. M. T.	19 F	M A II	RT		+75 +83			Smaller in CF_2 and CF_4		6 ribs removed. ECG abnormal because of inverted T waves in CF_2 and CF_4. Heart moderately displaced to left

Table 1—*continued*

Patient	Age and Sex	T.B. Diag.*	Collapse†	Heart Position‡ (cm.)	QRS Axis§	Changes in Limb Leads I and III: QRS	Changes in Limb Leads I and III: T Waves	Changes in Precordial Leads CF_2, CF_4, and CF_5: QRS	Changes in Precordial Leads CF_2, CF_4, and CF_5: T Waves	Remarks
T. J. B.	17 F	F A II	RT		+98 +103	QRS_3 larger		Larger in CF_2	More inverted in CF_2; smaller in CF_4 and CF_5	7 ribs removed. Heart slightly displaced to left
U. J. B.	27 M	F A II	RT		+22 +43	QRS_3 more upright	T_1 and T_3 taller	Larger in CF_4 and CF_5	Taller in CF_4 and CF_5	7 ribs removed. Heart slightly displaced to left
V. M. Z.	25 F	F A II	RT		+73 +71	QRS_1 larger	T_1 smaller		Smaller in CF_5	7 ribs removed. Heart moderately displaced to left
W. J. F.	41 M	F A II	RT		−5 +37	QRS_1 smaller; QRS_3 less inverted	T_1 smaller		Smaller in CF_5	7 ribs removed. Apex slightly displaced to left
X. R. G.	27 F	F A IV	LP		+103 +90	QRS_1 larger				Heart displaced to left before collapse. After collapse, displaced to right. Left border could not be visualized for measuring
Y. G. W.	37 M	M A II	LP	6.6 7.1	−15 −5	QRS_1 larger			Becomes inverted in CF_4 and CF_5 (was small and upright)	Curve becomes abnormal
Z. M. C.	46 F	M A II	LP	7.1 7.1	+56 +55		T_3 less inverted	Smaller in CF_2; larger in CF_4 and CF_5	Larger in CF_4 and CF_5	Change in character of P_1 and P_3
AA. M. C.	20 F	F A III	LP	4.2 4.3	+81 +69	QRS_1 larger; QRS_3 smaller	T_1 smaller	Larger and more upright in CF_4 and CF_5	Smaller in all leads	Illustrated. Marked change in CF_4 and CF_5
AB. J. R.	27 F	F A II	LP	4.8 5.0	+80 +67	QRS_1 larger and more upright; QRS_3 smaller	T_1 taller; T_3 more inverted	Smaller in all leads; more upright in CF_5	Less inverted in CF_2	

TABLE 1—*concluded*

Patient	Age and Sex	T. B. Diag.*	Col-lapse†	Heart Position‡	QRS Axis§	Changes in Limb Leads I and III		Changes in Precordial Leads CF_2, CF_4, and CF_5		Remarks
						QRS	T Waves	QRS	T Waves	
				(cm.)						
AC.	25	F A	LP	7.6	+48	QRS_1 larger	T_1 taller; T_3 inverted (was flat)		Smaller in CF_2	
A. G.	F	III		7.4	+22					
AD.	21	M A	RP	5.0	+72	QRS_1 less upright				
W. C.	F	II		4.4	+90					
AE.	23	M A	RP	8.1	+90			Less upright in CF_5		
A. W.	M	I		8.1	+96					
AF.	16	M A	RP		+65		T_3 inverted (was upright)			X-ray films not available
L. R.	F	II			+69					
AG.	23	M A	RP	6.0	+49	QRS_1 smaller; QRS_3 larger	T_1 smaller	Larger in CF_2; smaller in CF_4 and CF_5	Smaller in all leads	Illustrated
A. V.	F	II		5.0	+56					
AH.	42	F A	RP	6.0	+60	QRS_1 larger	T_1 taller	Smaller in CF_5	Taller in all leads	
I. B.	F	II		6.5	+66					
AI.	44	F A	RP	7.0	+15		T_1 smaller		More inverted in CF_2; inverted in CF_4 (was upright)	
J. C.	F	II		6.2	+10					

* The tuberculosis diagnosis follows the criteria given in "Diagnostic Standards and Classification of Tuberculosis," published by the National Tuberculosis Association, New York, 1940 edition; MA and FA denote moderately advanced and far advanced respectively, and the numerals I, II, III, and IV denote absent, slight, moderate, and severe symptoms, respectively.

† LT, left thoracoplasty; RT, right thoracoplasty; LP, left phrenemphraxis; RP, right phrenemphraxis.

‡ Lateral displacement of the heart was determined, in patients subjected to phrenic crush, by measuring in centimeters on the roentgenogram the lateral shift of the left contour of the cardiac shadow at the level of the superior border of the tenth rib, posteriorly. This point on the cardiac silhouette falls on the left ventricular contour. In patients with thoracoplasty, postoperative spinal curvature made this measurement meaningless. In these patients, cardiac shift was estimated by inspection of the roentgenogram. (See "Remarks" column.)

§ QRS axis (mean) was measured on the triaxial reference system of Bayley.

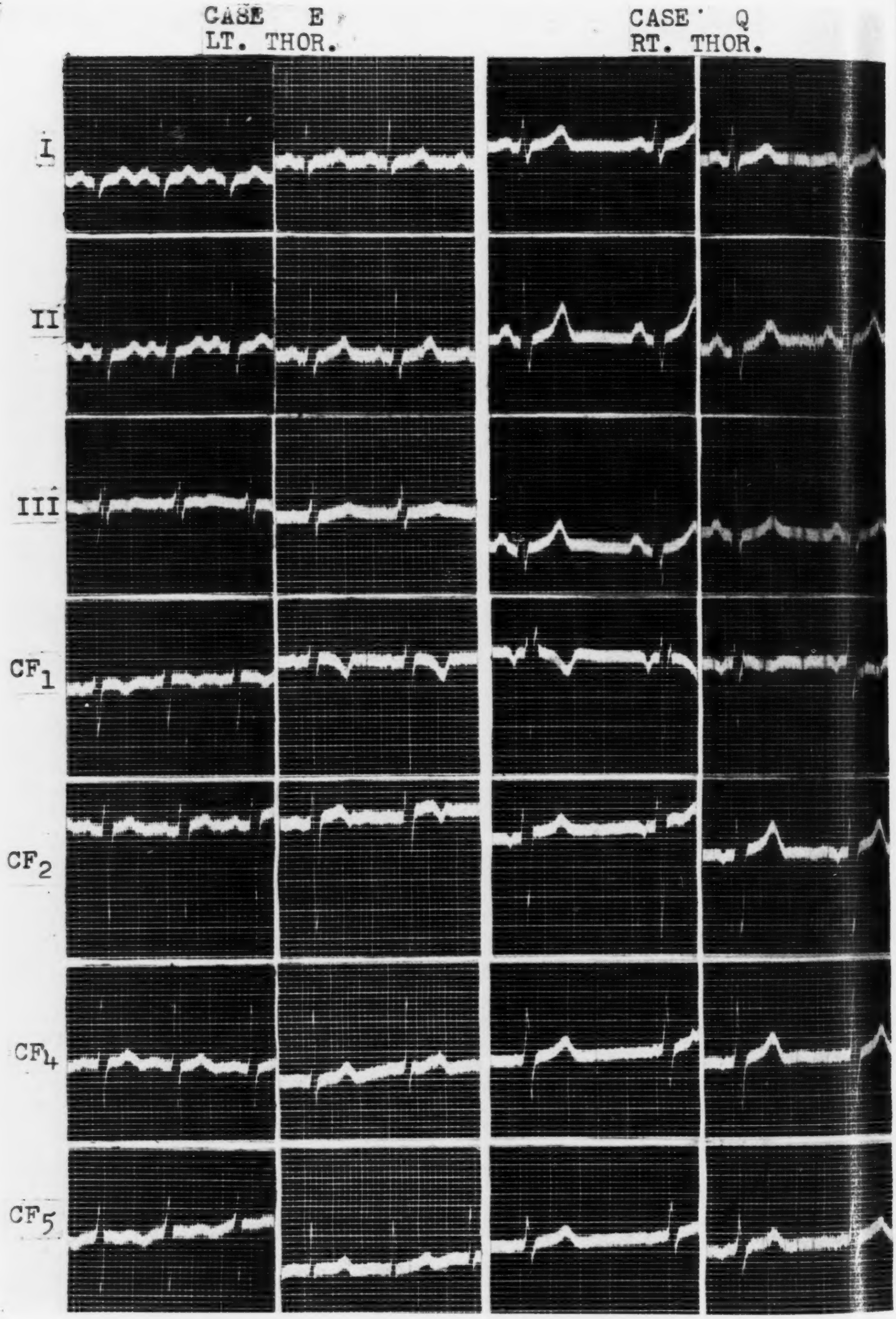
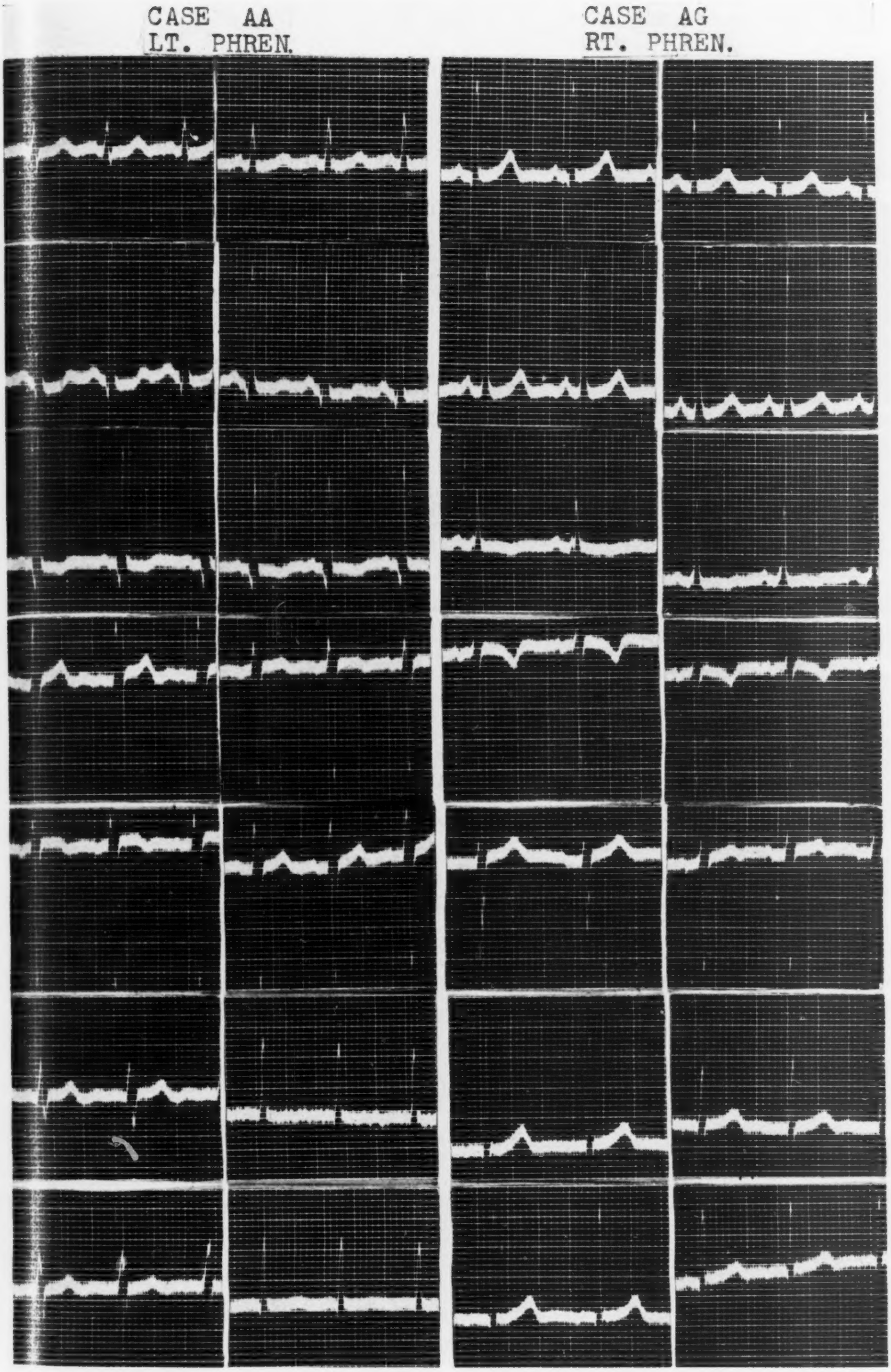


FIG. 1.—Electrocardiographic tracings from an illustrative case of each of the varieties of collapse procedure investigated. The first tracing in each series is the precollapse control record, and the



second is the tracing made after institution of the collapse. The cases were selected to show the average extent of changes encountered.

5. It seems probable that the most important factor in the genesis of the electrocardiographic changes is a change in the anatomic position of the heart.

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The Changes in Heart Size in Man During Partial Acclimatization to Simulated High Altitudes

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The heart size, as shown in serial roentgenograms, was determined in the case of 4 young volunteers who were continuously exposed to simulated high altitude over a period of one month. Sufficient adaptation occurred to allow them to remain at progressively higher altitudes up to 22,500 feet. A slight decrease in heart size was observed at all altitudes. This was thought to be due to decreased cardiac filling or smaller stroke volume or both. Doubt is expressed regarding the oft repeated statement that the heart in healthy persons exposed to anoxia readily increases in size.

ALTERATION in the size of the heart is regarded as one of the important indicators of the effect of anoxia on the circulatory system. For this reason, determinations of heart size have been made in persons exposed to a wide variety of conditions which have in common the effect of lowering the percentage of oxyhemoglobin in arterial blood. Thus, measurements have been made on persons living at high altitude, on aviators engaged in flying at great heights and on subjects exposed to low oxygen pressures in the laboratory. These studies, however, have not led to the development of a clear concept of the effect of anoxia on heart size. This is due in part to the limited number of observations which have been made, and in part to differences in professional opinion among the observers. Whether some of the differences are more apparent than real can be determined only after careful consideration of the circumstances under which the observations were made. These experimental variables fall into four main groups; namely, (1) individual differences between subjects, (2) variation in degree and duration of the anoxia, (3) environmental factors other than the anoxia, and (4) the methods employed in determining the heart size.

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It is the purpose of this paper to summarize the pertinent literature and to present some observations of our own. Our observations were made during the course of an experiment in which 4 healthy young men were subjected to simulated high altitudes in a decompression chamber over a period of one month. The size of the heart shadow, as revealed in teleroentgenograms, was determined at frequent intervals.

Historical Review

The published reports can be arbitrarily grouped in three main categories, namely, (1) observations on subjects exposed to acute anoxia, (2) observations on fully acclimatized residents at high altitude (chronic anoxia), and (3) observations on persons partially acclimatized to high altitude (varying degrees of adaptation to anoxia).

Acute anoxia. There are conflicting reports on the effect of acute anoxia on heart size; some observers[1, 2] state that the heart may readily dilate, others[3-5] that the heart size may increase or decrease, while still others[6, 7] state that there is no change.

The best evidence strongly supports the view that little or no alteration in size occurs. The small alterations observed may be explained all or in part by the variations in degree of filling. The slight enlargement of the heart which has been noted may be due to a compensatory increase in stroke volume in persons making a good adjustment to acute anoxia. The slight decrease in heart size which has been noted is thought to be due to a decrease in stroke volume in persons showing signs of peripheral circulatory failure. Stated differently, the evidence favors the view that primary heart failure leading to cardiac dilatation does not occur when healthy persons are exposed to anoxia but that the slight

changes in heart size reflect alterations in the state of the circulation.

Full acclimatization to high altitude. The studies of Miranda and Rotta[8] and of Kerwin[9] indicate that in the majority of persons, long resident at high altitude, there is some degree of cardiac enlargement which is predominantly right sided.

Partial acclimatization to high altitude. Between the extremes of sudden exposure of persons to acute anoxia or decompression on the one hand, and prolonged residence at great elevations on the other, there is a wide range in degree of adaptation to anoxia or high altitude. Numerous observations are on record of these effects on heart size. Some of these observations are the result of deliberate, planned study while others are merely chance or incidental findings, ofttimes by observers lacking in professional skill and judgment. The results are not always easily evaluated and the material as a whole does not lend itself to concise summarization.

It is remarkable that investigations[10-13] on the effects of flying on heart size have led to the conclusion that in many pilots intermittent exposure to anoxia results in cardiac enlargement. It seems improbable that ascents, however, frequent, would cause cardiac enlargement in healthy persons. The cardiovascular adjustments at moderate altitudes do not throw a great burden on the heart when the individual is at rest and the direct effect of anoxia on the heart muscle is, in all probability, not very great. Factors other than flying need to be rigidly controlled; the suggestion of Gomez[14] that slight cardiac enlargement may be observed in all military personnel under training is pertinent.

There are a number of references to be found on the effect of limited sojourns at high altitude on heart size. In the case of mountaineers or soldiers whose amount of physical work was great, Sommerwell,[15] Hingston,[16] and Kaufmann and Meyer[17] all found marked increases in heart size in persons under their observation. These observations were made using the percussion method and, often, under the rigorous conditions which prevail in a tent or on the mountainside. Under these circumstances, not only are precise measurements difficult, but also the observers themselves are hampered by oxygen lack.

Measurements of heart size have also been made on temporary residents at high altitude who did not engage in heavy work. Barcroft[18] measured the heart size from radiograms taken on 5 members of his Andean expedition in 1921–22. A comparison of the measurements made from radiograms taken at sea level, within two hours after arrival at Oroya (12, 178 ft.) and after two and three weeks, residence at Cerro de Pasco (14,208 feet) showed that at no time was there an increase in heart size at high altitude. In 3 members there was a slight but definite decrease; one member showed a probable slight decrease and one other no change in heart size.

Talbott and Dill[19] made observations on healthy persons living at the extremely high altitude of 17,500 feet. The length of residence at high altitude varied from two to fourteen years. These observers found that the heart size, as determined by percussion, was not increased above normal. The limitations of their method were recognized.

Gomez[14] measured the transverse diameter of the heart by means of teleroentgenograms in 480 civilian inhabitants of Bogotá, which is 8,016 feet above sea level. Some of his subjects were natives, the others had resided at high altitude for periods ranging from days to years. His findings were similar to the standards established by Ungerleider and Clark[20] for persons living at sea level.

From the observations just presented it is apparent that much more work remains to be done before final conclusions can be drawn with regard to the effect of altitude on heart size in partially acclimatized individuals. Some of the evidence suggests that in the very early stages there is a slight decrease in heart size, at least in persons not undertaking heavy physical work. The observations by mountaineers that the heart enlarges to a marked degree in men doing hard work at high altitude are of doubtful accuracy. There is reliable evidence that persons may reside at moderately high altitudes for varying periods of time without demonstrable cardiac enlargement. However, during some period in the process of full acclimatization, enlargement must result in view of the findings that lifelong dwellers at high altitude have large hearts.

Experimental Procedure

Our experiment was carried out on 4 healthy men, aged 19 to 27 years, who lived in a decompression chamber continuously for thirty-five days. After a three day control period at sea level, the atmospheric pressure within the chamber was reduced to simulate an ascent to high altitude.* The daily change in altitude is shown in chart 1. Below 15,000 feet, all increases in altitude were made at the rate of 1,000 feet a minute, but above 15,000 feet, the rate was reduced to 250 feet an hour. During the fourth week the subjects were able to remain at 22,500 feet but were more comfortable 1,500 feet lower. Toward the end of the experiment the subjects were taken to 29,000 feet without supplementary oxygen, and to 50,000 feet when breathing 100 per cent oxygen.

The environmental factors in addition to decompression were carefully controlled and

* Hereafter the word altitude will be used instead of simulated altitude for simplicity of expression.

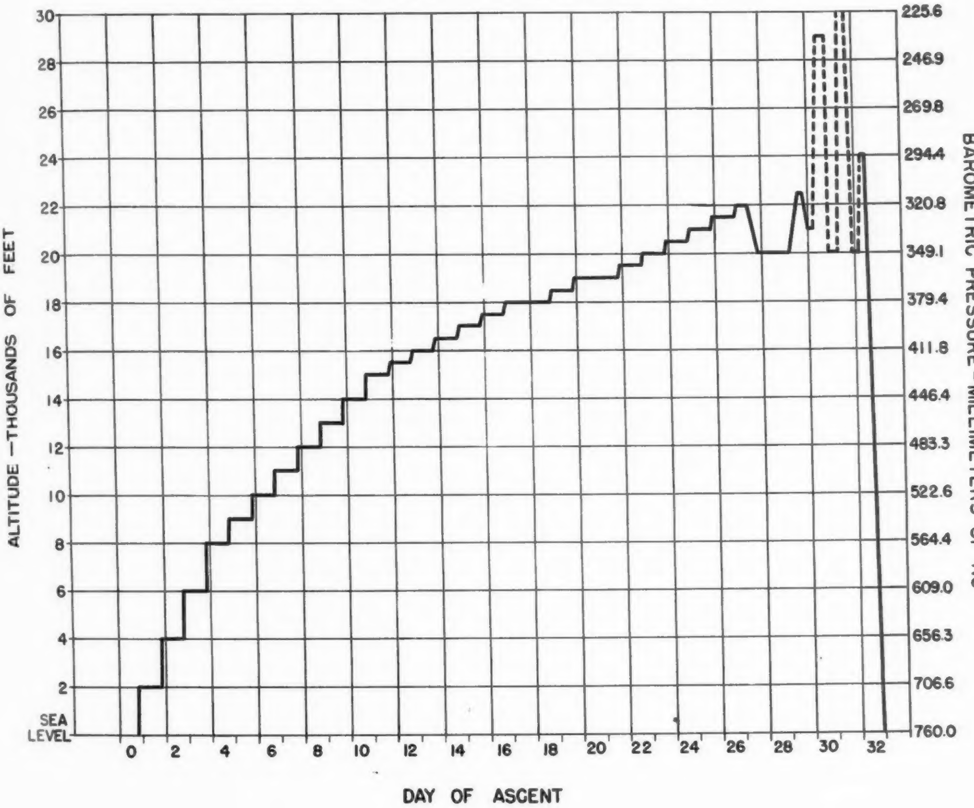
recorded. Temperature within the chamber was maintained between 65 and 75 F. Regular exercise on a stationary bicycle was encouraged; one subject (McN) averaged 250,000 foot pounds of work daily but the other 3 did much less. The men were given their choice of food. Three of the subjects smoked in moderation; the fourth (McN) abstained. The reader may refer to previous reports for details of experimental procedure.[21]

Two series of teleroentgenograms were made, one within and one without the decompression chamber. The latter series was made at the U. S. Naval Hospital, Pensacola, and consisted of teleroentgenograms of the chest taken both before and after the subjects were decompressed, a single exception to this was the omission of the x-ray examination in the case of one subject (M) prior to his entering the chamber.

All teleroentgenograms within the chamber were made with a 30-milliampere portable apparatus. All of the films were taken by the same operator, using similar technic on each occasion. The subjects stood facing away from the x-ray tube at a target distance of 6 feet. The film was exposed for one-half second while the subject held his breath after full inspiration. One or more teleroentgenograms were made at sea level and on eight representative experimental days.

Measurements of the cardiac shadow were made on every teleroentgenogram obtained from 3 subjects. In the case of one subject (H) no measurements were made because the right border of the heart shadow was obscured by

CHART 1.—Simulated altitudes to which subjects were exposed



the shadow of the spine. The measurements were based on the procedure recommended by Ungerleider and Clark[20] and Ungerleider and Gubner.[22]

be made. The changes in the long and broad diameters paralleled the changes in transverse diameter but there were exceptions to this. The very slight amount of rotation of the

TABLE 1.—*Heart Shadow Measurements from Teleroentgenograms of Three Subjects during Partial Acclimatization to Simulated High Altitudes*

SUBJECT	DATE	SIMULATED ALTITUDE (FEET)	ROTATION	DISTANCE BETWEEN 9TH. RIB AND DIAPH.		INTERNAL DIAMETER THORAX	MEASUREMENT OF HEART SHADOW				AORTIC PEDICLE DIAMETER
				RIGHT	LEFT		TRANSVERSE DIAMETER	LONG DIAMETER	BROAD DIAMETER	FRONTAL AREA	
McN[redacted]	June 25^x	Sea Level	V. Sl. Left	4.4	6.2	33.5	12.4	15.7	11.3	139.	5.1
	28	Sea Level	None	3.7	4.6	33.3	12.6	16.2	11.5	148.	4.9
	28	Sea Level	None	5.5	6.4	33.2	12.6	16.3	11.3	145.	5.1
	July 8	12,000	V. Sl. Left	6.4	8.3	32.7	11.7	16.2	11.0	140.	4.9
	17	18,000	Sl. Left	7.0	8.4	32.4	11.8	15.7	11.0	136.	5.2
	22	19,500	V. Sl. Left	6.7	8.5	33.2	11.4	14.7	10.8	125.	4.9
	24	20,500	None	7.5	9.1	32.4	11.5	15.4	11.0	133.	5.2
	26	21,000	None	7.1	8.8	32.3	11.6	15.4	11.2	135.	5.1
	29	22,500	None	6.8	8.4	32.2	11.7	15.3	11.3	136.	5.0
	Aug. 1	20,000	V. Sl. Left	5.8	7.8	32.0	11.4	15.5	10.7	130.	5.2
	1	24,000	None	5.4	6.9	32.5	12.0	15.4	11.1	134.	5.1
	3^x	Sea Level	None	7.0	8.9	33.5	12.8	15.2	11.3	135.	4.9
M[redacted]	June 28	Sea Level	None	6.4	8.3	30.3	10.8	13.8	10.0	108.	5.5
	July 8	12,000	None	5.7	8.2	32.4	11.2	13.6	10.6	113.	5.6
	17	18,000	V. Sl. Left	7.0	9.1	30.9	10.1	13.5	9.8	104.	5.5
	22	19,500	None	6.5	9.3	31.0	10.4	13.4	10.3	108.	5.8
	24	20,500	None	7.2	9.5	32.1	10.4	13.7	10.1	109.	5.7
	26	21,000	None	6.6	9.0	31.0	10.3	13.5	10.3	109.	5.5
	29	22,500	None	6.8	8.9	31.0	10.5	13.4	10.2	107.	5.7
	Aug. 1	20,000	V. Sl. Left	6.8	9.3	32.1	10.3	13.3	10.3	108.	5.5
	1	24,000	None	6.9	9.4	32.3	10.7	13.8	10.6	115.	6.0
	3^x	Sea Level	None	6.2	8.8	32.0	11.1	14.4	11.2	127.	5.4
W[redacted]	June 19^x	Sea Level	None	7.4	8.2	27.9	11.5	14.4	9.9	112.	5.2
	28	Sea Level	V. Sl. Right	2.5	2.7	27.8	11.6	13.9	9.3	102.	5.1
	28	Sea Level	V. Sl. Right	2.3	2.6	27.8	11.3	13.6	9.7	104.	4.8
	July 8	12,000	None	6.1	5.5	27.2	11.0	14.5	9.4	107.	5.1
	17	18,000	V. Sl. Left	5.4	6.0	27.3	10.6	14.5	9.1	104.	5.6
	22	19,500	V. Sl. Left	4.3	5.2	26.7	10.5	14.4	9.5	107.	5.0
	24	20,500	None	4.8	5.8	26.7	10.5	14.7	9.1	105.	5.7
	26	21,000	V. Sl. Right	5.0	6.4	26.7	10.3	14.5	9.5	108.	5.1
	29	22,500	None	3.7	4.7	27.2	10.9	14.1	9.4	104.	5.3
	Aug. 1	20,000	None	4.4	5.5	27.2	10.4	13.2	9.4	97.	4.9
	1	24,000	None	4.1	4.7	27.3	10.5	13.4	9.3	98.	4.9
	3^x	Sea Level	None	5.4	6.2	27.8	11.8	14.7	10.3	119.	5.6

X= U. S. NAVAL HOSPITAL FILM
ALL HEART MEASUREMENTS IN cm. (EXCEPT FRONTAL AREA WHICH IS IN sq. cm.)

RESULTS

Table 1 summarizes the data obtained from the teleroentgenograms. In analyzing the results, chief reliance was placed on the transverse diameter measurements because of the exactness with which this measurement could

thorax from the true postero-anterior position did not appear to be important. In general, the results are consistent in showing that the heart shadow decreased slightly in size while the subjects were exposed to reduced atmospheric pressures. With a single exception (M, July 8) the transverse cardiac diameter, the

most reliable measurement, was always smaller in the teleroentgenograms made at high altitudes than in those made at sea level. It is further to be noted that there was no consistent decrease in size of the heart shadow in relation to increasing altitude, although individual exceptions to this will be pointed out below.

In the case of Subject McN the measurements of heart shadow taken from the four films obtained at sea level showed little variation despite the fact that the position of the diaphragm differed considerably. There was a tendency for the heart shadow to become progressively smaller with increasing altitude up chamber, with the one made at the hospital after the experiment was over, showed fairly good agreement. This agreement was good for the transverse diameter, fair for the long diameter, but poor for the broad diameter. At 12,000 feet the size of the heart shadow was about the same as the average at sea level. At 18,000 feet the heart shadow was slightly smaller (fig. 2, *a*) and thereafter the changes were probably insignificant until the return was made to sea level. At the time of ascent from 20,000 to 24,000 feet there was a very slight increase in the size of the heart shadow (fig. 2, *b*) but not exceeding that at sea level.

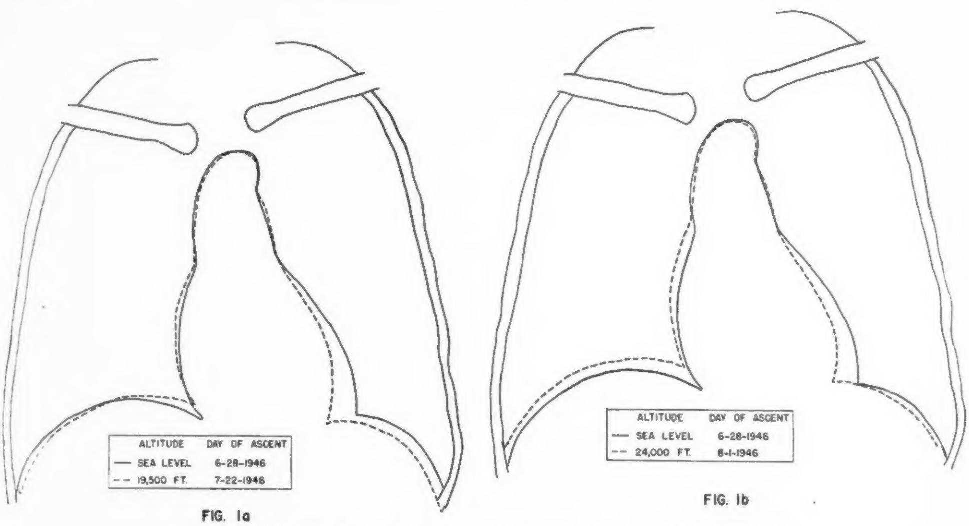


FIG. 1.—Change in cardiac silhouette with altitude (Subject McN)

to 19,500 feet. This maximum decrease is illustrated in figure 1, *a*. Thereafter, the changes were insignificant until the last experimental day when the subject ascended from 20,000 to 24,000 feet. The transverse cardiac diameter in the film obtained at 24,000 feet (fig. 1, *b*) was greater than it was in any other film obtained at high altitude, although it was still smaller than any of the comparable measurements made from films obtained at sea level.

In the case of Subject M, only one teleroentgenogram was obtained at sea level prior to ascent in the chamber because he was a last-minute substitute for another subject. A comparison of this film, which was made in the

There were four films taken at sea level on the third subject, W. The measurements of the heart shadow were similar in all four but the agreement was even closer if the radiograms made in the hospital and in the decompression chamber were separately compared. With increasing altitude there was a progressive decrease in transverse diameter up to the altitude of 21,000 feet. Three days later, at 22,500 feet, the transverse diameter was slightly greater again; the cardiac silhouette at this time is shown in figure 3, *b*. It should be noted that the changes in the long and broad diameters were smaller than in the transverse diameter.

Although exact measurements were not made in the case of the fourth subject, the teleroentgenograms were carefully reviewed. Inasmuch as a slight increase in the projection of the heart shadow to the right of the midline would have allowed the right border of the heart to become visible, it may be assumed that such an increase did not occur. Thus, there was fairly good evidence for concluding that the heart shadow at least did not *increase* appreciably in size.

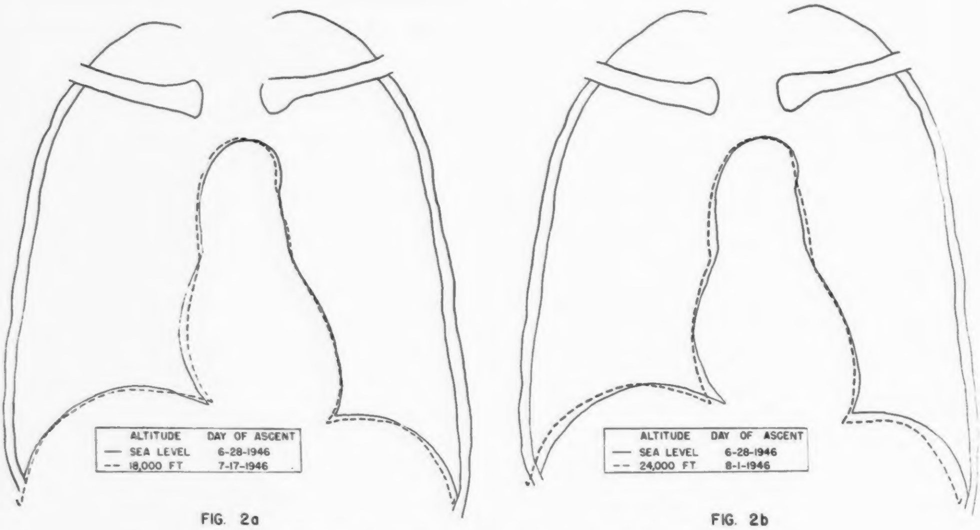


FIG. 2a FIG. 2b

FIG. 2.—Change in cardiac silhouette with altitude (Subject M)

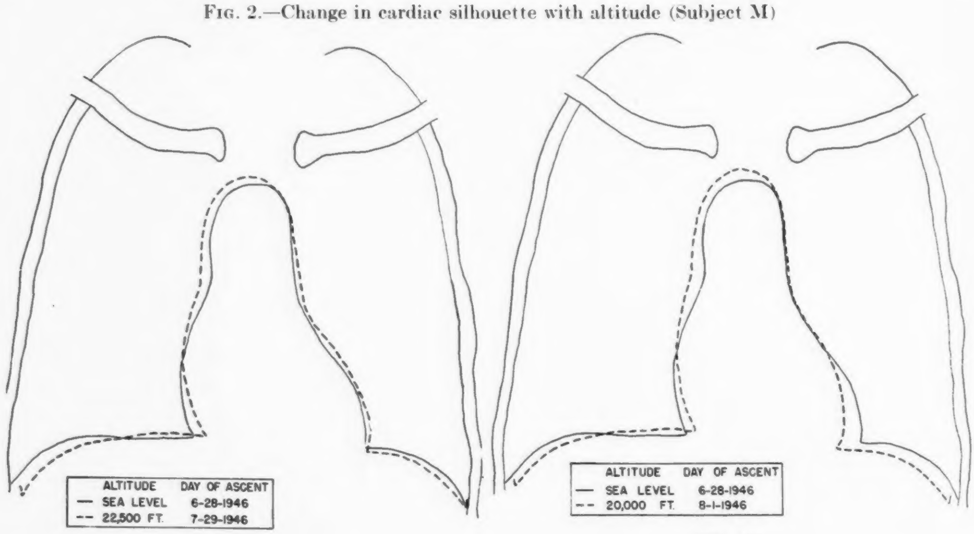


FIG. 3a FIG. 3b

FIG. 3.—Change in cardiac silhouette with altitude (Subject W)

Discussion

There is no doubt that the heart shadow, as revealed in serial teleroentgenograms, was smaller when the subjects of our experiment were at simulated high altitudes as compared

with sea level. This decrease in size was slight but it was too consistent to be explained by chance. There was only a slight tendency for these changes in heart shadow size to follow a pattern. This may be partly explained by the fact that the changes were small and also by the fact that the effects of increasing altitude were offset by acclimatization or adaptation.

The next question requiring consideration is whether the observed decrease in *heart shadow size* indicated an actual or only an apparent decrease in *heart size*. The following reasons are given in support of the opinion that the heart in our subjects was actually smaller at high altitude. First, the extent of the decrease in heart shadow size in some instances could not easily be explained on the basis of test-retest reliability of the procedure or on the basis of alteration in shape and position of the heart. Second, with regard to the position of the subject, there was never more than slight rotation of the thorax with reference to the direction of the roentgen rays. In the case of Subject W (table 1) it was possible to compare left and right rotation and in both instances the heart shadow size at altitude was smaller than at sea level. Even if all films showing rotation were discarded, the results would not be different. Third, changes in the level of the diaphragm cannot adequately account for the decreases in the heart shadow size observed. The variations in the level of the diaphragm in our subjects were no greater at altitude than at sea level. Moreover, inasmuch as our subjects were not rapidly decompressed the expansion of intestinal gases with its effect on the diaphragm and position of the heart was not a factor.

Assuming, then, that an actual decrease in the size of the heart occurred, how is it to be explained? Our data do not bear directly on this question; indeed, it would be difficult, if not impossible, to give a definitive answer to this question from the results of experiments on man. The decrease in heart size might have been due to a direct effect of anoxia on the myocardium or secondary to changes in the peripheral circulation.

It should be mentioned in this regard that our subjects were standing while the teleroentgenograms were being made and this may have been an important additional factor. Circulatory changes induced simply by a shift from the recumbent to the upright position may be sufficient to cause a measurable decrease in heart size.[23] We have observed even greater decrease in healthy subjects in whom peripheral circulatory failure was induced by nitroglycerine.[24]

In relating one's findings to those of other workers, it is always necessary to bear in mind whatever differences existed in experimental procedure. Thus our results may be compared in only a limited way with the results of most experiments on acute anoxia. However, insofar as a comparison is allowable, our findings are in general accord with those of other investigators who found no increase in heart size when healthy subjects were decompressed.

Our subjects were exposed to decreased oxygen pressure for a much longer period of time than were many of the aviators referred to above, who were considered to have developed cardiac enlargement as the result of exposure to anoxia. Although these findings cannot be directly compared because of the fact that, in the case of the aviators, the exposures were intermittent over a relatively long time, yet our findings tend to cast some doubt on the statement that moderate anoxia can so readily cause an increase in heart size.

Our findings are in agreement with those of Barcroft,[18] mentioned above, who found a slight decrease in heart size in 4 out of 5 members of his expedition while they resided at high altitude. The amount of work our subjects performed in the decompression chamber was probably less than the exertions performed by members of Barcroft's party. A possible exception was Subject McN who did 250,000 foot pounds of work a day, the equivalent of climbing 1,900 feet.

Because of the limited amount of exercise performed by our subjects the strain on their hearts was much less than that incurred by mountaineers and by many residents at high altitude. Hence, our results cannot be compared with the observations made under these circumstances.

Summary and Conclusions

1. Four healthy young men were partially acclimatized over a period of one month to simulated high altitude in a decompression chamber. During the fourth week the subjects were able to remain at 22,500 feet and on occasion were taken to higher altitudes for short periods.

2. The size of the heart shadow, as revealed in teleroentgenograms, was determined at frequent intervals. Measurements of the films of one subject were not made because the right border of the heart was obscured by the shadow of the spine.

3. The results indicate that the heart shadow decreased slightly in size when the subjects were exposed to reduced atmospheric pressures.

4. There is little reason to doubt but that this decrease in heart shadow size indicated an actual rather than simply an apparent decrease in heart size.

5. Although our data do not directly bear on the cause of the decrease in heart size, it is believed to be due to decreased cardiac filling or smaller stroke volume or both.

6. It is concluded that during an early stage of acclimatization to severe anoxia under the conditions of our experiment, dilatation of the heart does not occur, but rather the heart may decrease slightly in size.

7. Some of the pertinent literature is reviewed and may be summarized under the following three headings: (a) With regard to the effect of acute anoxia on heart size, the evidence suggests that slight, if any, change occurs in healthy subjects up to the point of collapse. The reports stating that marked cardiac dilatation may occur are open to criticism; unfortunately, some of these are widely quoted in the medical literature. (b) With regard to full acclimatization, there is evidence that lifelong residents at high altitude have larger hearts than residents at sea level. (c) With regard to adaptation to anoxia or partial acclimatization to high altitude, the evidence is incomplete. The reports that aviators develop cardiac enlargement following repeated short exposures to high altitude are open to serious doubt. The observation that mountain climbers may develop marked cardiac enlargement has never been confirmed by properly trained investigators. The evidence suggests that often in the early stages of acclimatization the heart may decrease slightly in size. There is evidence also that even in persons residing for relatively long periods at high altitude, the heart does not enlarge.

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The Effect of an Ordinary Meal on the Electrocardiogram. Normal Standards in Middle-Aged Men and Women

By Ernst Simonson, M.D., and Ancel Keys, Ph.D.

In previous studies on young men it was found that definite changes in the electrocardiogram are produced by an ordinary meal. This work has been extended with a larger series of older men and women. In general, the results confirm the previous studies but an age trend was found in some items. The combined material allowed an analysis of the correlations between the changes in the various items of measurement and more detailed consideration of the physiologic mechanisms involved. Normal fiducial limits for the changes induced by a meal were calculated to provide a basis of discrimination between normal and abnormal responses.

IN NORMAL young men an ordinary meal produces statistically significant changes in various electrocardiographic items. In some cardiac patients the changes in the electrocardiogram induced by a meal were even more striking than in normal men[2, 3] and it seemed possible that a useful functional test might be developed by utilizing a meal as a simple "stress." For this purpose, normal standards, properly defined statistically, would be essential. It was doubtful, whether the data on the 12 normal young men previously studied[1] would be adequate for this experiment, not only because of the small number of individuals, but more particularly because of the restricted age range represented. The majority of patients with whom it might be desirable to employ such a test are in the age range of 40 years or older and proper normal standards for them must be obtained from a reference group of comparable age. This requirement is underscored by our recent experience with 500 "normal" men[4] in whom very definite age trends emerged from quantitative analysis of basal (without meal) electrocardiograms.[4a]

Subjects

The main experimental group consisted of 42 men, mostly "white collar" workers between the ages of 45 and 55 years. They were without significant medical complaints and were selected from a larger group[4] as being fully normal on the basis of a thorough clinical examination, including electrocardiography and radiography. As criteria for the normal limits of the electrocardiogram the data of Katz and associates[5] were used; these differ but slightly from the normal limits given in various standard texts on electrocardiography. In addition we used the recent data of Sokolow and Lyon[6] as criterion for abnormally high voltage.

Identical studies were made on 12 women between the ages of 39 and 59 years. These women likewise were without significant medical complaints and were judged to be "normal" on the basis of the history and a routine electrocardiographic examination.

Experimental Procedure

The pre-meal electrocardiograms were taken in the morning, about one hour after the subjects had arrived in the laboratory without breakfast, and after fifteen to twenty minutes of supine rest. A second series of electrocardiograms was taken fifteen to thirty minutes (including a few minutes of supine rest) after a lunch of 1260 calories. No smoking was allowed. The three standard leads, V_1, V_2, V_4, and CF_4 were taken before and after the meal. The spots for the chest leads were marked with a skin marking pencil to eliminate variability in the position of the electrode before and after the meal.

A total of 36 electrocardiographic items was measured. As a criterion of arrhythmia the difference between the smallest and largest R-R interval (Δ Max.–Min. R-R) in a given record was used. The average heart rate was calculated from 10 beats, and the average Q-T interval from 5 beats, usually in Lead II. The value of K_{QT} was calculated as the

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quotient of the average Q-T interval divided by the square root of R-R. Σ QRS and Σ T are the sum of the QRS and T deflections in the three standard leads. The limitations of this procedure are obvious, but Σ QRS and Σ T have been found to be practically useful as an index of voltage changes.[1, 7] The QRS axis and T axis were measured by means of Dieuaide's diagram. Both Lead CF_4 and Lead V_4 were analyzed but the changes in them after the meal were nearly identical so only the data for V_4 are given here.

Results

The more important findings in the 42 middle-aged normal men are summarized in table 1. The data for V_2 are omitted because they added little to the information obtained with V_1 and V_4. All potentials are given in terms of standardized mm. of amplitude (1 mm. = 0.1 mv).

The majority of the items showed changes after a meal which are statistically highly significant, that is they would occur by chance alone less than once in a hundred cases ($p = <0.01$); the appraisal of significance here was made by applying the F test to the before and after data for each item. The only items which showed less consistent (i.e., nonsignificant) changes are Q_1, Q_3, and the amplitudes of R, S, and T in Lead V_1.

The mean changes of the P-R interval, of the QRS interval, of the Q wave in all standard leads, of $S\text{-}T_1$ and $S\text{-}T_3$, of ΔMax.-Min. R-R, K_{QT}, QRS axis, T axis, R wave and S wave in V_1 and V_4, and $T\text{-}V_1$ are comparatively small, not exceeding the intraindividual S.D.[8] However, many of these changes are consistent (i.e., statistically significant).*

The results confirm our previous findings on young men.[1] A rather consistent picture can be seen in normal men, such that we may speak with some confidence about a normal electrocardiographic response to a meal.

In spite of very substantial and statistically highly significant changes in various items, the postmeal electrocardiograms all remained within the generally accepted limits of normality and the same was also true for the group of younger men. This can be simply explained by the fact that in the collection of normal standard material the intake of meals has been ignored in the standardization of the procedure.

On the basis of the material presented in table 1 it is possible to define, quantitatively, the limits of the normal response to a meal and thereby to discern abnormality when it occurs. In table 1 are given the expected normal limits for 90 per cent and for 98 per cent of any population for which these men are a valid sample. For example, we can say that when an ordinary meal produces a rise in R_2 of 4.5 mm. then the result is "possibly abnormal," since an increase as large as this would occur in only 5 per cent of a normal population. And a decrease in R_2 of 1.7 mm. could be properly labeled as "very probably abnormal," because a decline of this magnitude would be expected in only 1 per cent of the normal reference population. Wider ranges, for instance for 99.8 per cent of normal population, can be easily calculated from the means and standard deviations in table 2 .

For these purposes those items which, in normal man, are relatively unaffected by a meal may be as useful as those which normally exhibit a large change. The fact that the postmeal changes in normal men always occur within the limits usually accepted as normal may also be utilized as a criterion for an abnormal response.

Relation between Pre- and Postmeal Values. So far, the changes produced by a meal have been discussed without reference to the characteristics of the electrocardiogram before the meal; only the absolute magnitudes of the changes have been considered. However, it is conceivable, and even probable, that the extent of the meal change should be somewhat affected by the pre-meal characteristics. Exploration by means of correlation surfaces seems to verify this supposition for at least some items. The T-wave amplitudes, for example, showed a clear correlation between the values before the meal and the changes after the meal (fig. 1). It appears that the extent of the postmeal change in the QRS axis (fig. 2) is related to the angle of the pre-meal axis up to about 50 degrees, but when the pre-meal angle was

* Statistical significance expresses the consistency, but not the magnitude of changes.

greater than 50 degrees (up to 94 degrees), the postmeal value was nearly constant. It is of interest that there was no apparent relation at any level between the angle of the T axis before the meal and the postmeal change.

Obviously, for those items in which the extent of the change produced by the meal is definitely related to the pre-meal level of the items, precise standards should take account

Table 1.—*Changes in the Electrocardiogram after a Meal. (Means and standard deviations (S.D.) of the difference, postmeal minus pre-meal values, for 42 normal men aged 45 to 55, together with the predicted normal limits for 90 per cent and 98 per cent of any population for which these men may be considered a valid sample.)*

Item	Change		Normal Limits	
	Mean	S.D.±	90%	98%
Heart rate	+11.09	2.09	+7.7 to +14.5	+6.2 to +16.0
ΔMax-min R-R × 100	−1.3	4.0	−8.0 " +5.0	−11.0 " +8.0
P-R int. × 100	−0.5	1.0	−2.0 " +1.0	−3.0 " +2.0
QRS int. × 100	+0.4	1.0	−1.0 " +1.0	−1.0 " +2.0
K_{QT} × 100	+1.5	2.0	−1.0 " +4.0	−2.0 " +5.0
Q_1	−0.03	0.13	−0.4 " +0.2	−0.4 " +0.3
Q_2	+0.06	0.20	−0.3 " +0.4	−0.4 " +0.5
Q_3	−0.04	0.39	−0.7 " +0.6	−1.0 " +0.9
R_2	+1.94	1.53	−0.6 " +4.5	−1.6 " +5.6
S_2	−0.28	0.39	−0.9 " +0.4	−1.2 " +0.6
Σ QRS	+3.58	3.48	−2.1 " +10.3	−4.5 " +11.7
S-T_1	−0.07	0.15	−0.3 " +0.2	−0.4 " +0.3
S-T_2	−0.23	0.34	−0.8 " +0.3	−1.0 " +0.6
S-T_3	−0.08	0.22	−0.4 " +0.3	−0.6 " +0.4
T_1	−0.86	0.61	−1.9 " +0.2	−2.3 " +0.6
T_2	−0.90	0.64	−2.0 " +0.2	−2.4 " +0.6
Σ T	−1.89	1.28	−4.0 " +0.2	−4.9 " +1.1
QRS axis°	+5.52	12.51	−15 " +26	−24 " +35
T axis°	+3.02	8.87	−12 " +18	−17 " +23
R-V_1	+0.14	0.55	−0.8 " +1.0	−1.1 " +1.4
S-V_1	+0.31	1.86	−2.8 " +3.1	−4.0 " +4.7
T-V_1	+0.41	2.43	−3.6 " +4.4	−5.4 " +6.2
R-V_4	+0.68	2.30	−3.1 " +4.4	−4.7 " +6.1
S-V_4	+0.57	1.71	−1.2 " +3.4	−3.4 " +4.6
T-V_4	−2.56	1.33	−4.7 " +0.4	−5.6 " +0.5

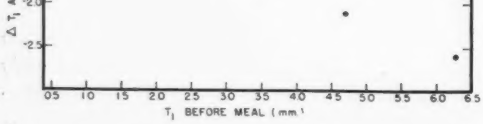

Fig. 1.—Changes of T_1 (ordinate) after the meal versus the initial T_1 before the meal (abscissa) in 42 subjects.

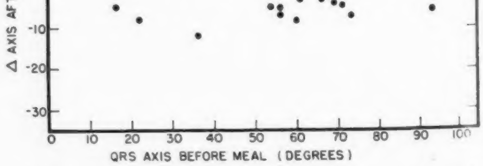

Fig. 2.—Changes of the QRS axis after the meal (ordinate) versus the value for the QRS axis before the meal (abscissa) in 42 subjects.

of the pre-meal level. For this purpose we have divided the group into roughly equal halves so as to obtain subgroups with relatively high and relatively low pre-meal values for the several items; the point of division was made on the basis of the apparent trend and distribution of values in the scatter diagrams. Statistical comparison of the subgroups by means of the F test showed that for each item listed in table 2 the mean change resulting from the meal differed highly significantly for the subgroups ($p = <0.01$ except for R_2 where $p = <0.05$). Table 2 shows the mean changes, S. D., and the expected normal range limits, as in table 1, but adjusted for the pre-meal level.

TABLE 2.—*Relation between the Pre-meal Value and the Change Induced by a Meal. (For each item the 42 normal men were divided into two subgroups according to the pre-meal division values indicated. Expected normal limits for 90 and for 98 per cent of the population of middle-aged men for the changes induced by a meal. Values calculated according to the pre-meal level for each of the electrocardiographic items.)*

Item	R_2	T_1	T_2	Σ T	T-V_4	QRS Axis
Pre-meal value above	7.0	2.5	3.5	6.0	7.0	50°
Mean Δ	2.42	−1.35	−1.41	−2.57	−3.42	−1.33°
S.D., ±	1.58	0.57	0.76	1.40	1.43	4.39°
90% limits	−0.4	−2.3	−2.7	−4.0	−5.8	−8.5
	+5.0	−0.4	−0.2	+0.3	−1.1	+5.9
98% limits	−1.3	−2.7	−3.2	−5.8	−6.8	−11.6
	+7.1	0	+0.4	+0.7	+0.1	+8.9
Pre-meal value below	7.0	2.5	3.5	6.0	7.0	50°
Mean Δ	1.31	−0.58	−0.67	−1.27	−1.95	12.38°
S.D., ±	1.24	0.45	0.43	0.79	0.86	14.1°
90% limits	−0.7	−1.3	−1.4	−2.6	−3.3	−10.6
	+3.3	+0.2	0	0	−0.5	+35.5
98% limits	−1.6	−1.6	−1.7	−3.6	−4.0	−20.3
	+4.2	+0.5	+0.3	+0.6	+0.1	+45.1

The Meal Effect in Women. Table 3 is largely the counterpart, for women, of table 1; it summarizes the major findings on our 12 normal women between the ages of 39 and 59 years. On the whole, the changes are very similar to those occurring in older men (table 1). While there are some numerical differences between the values in tables 1 and 3, the total material is too small to judge whether these differences are really important. The most prominent apparent differences between the men and women are in the heart rate and in the T axis. In older men any decrease in the heart rate after a meal would be abnormal ($p = <0.01$). In women a decrease of 2 beats per minute would

TABLE 3.—*Changes in the Electrocardiogram after a Meal. (Means before and mean change after the meal for 12 normal women aged 39 to 59 years, together with predicted normal limits as in table 1 for middle-aged men.)*

Item	Before meal	Change: Mean	Change: S.D.	Normal 90%		Limits 98%	
Heart rate	72.42	+4.00	4.11	−2.7	+10.7	−5.4	+13.5
K_{QT} × 100	39.6	+0.8	1.4	−1.0	+3.0	−2.0	+4.0
R_2	7.80	+1.56	1.12	−0.4	+3.5	−1.1	+4.3
Σ QRS	20.03	+3.14	2.11	−0.3	+6.6	−1.7	+8.0
T_1	1.96	−0.45	0.46	−1.2	+0.3	−1.5	+0.6
T_2	2.47	−0.81	0.42	−1.5	−0.1	−1.8	+0.2
Σ T	5.05	−1.29	0.86	−2.7	+0.1	−3.3	+6.9
T − V_4	3.59	−1.13	0.61	−2.1	−0.1	−2.5	+0.3
QRS axis	41.8	+6.3	11.1	−12	+24	−19	+32
T axis	39.7	−8.5	19.6	−41	+24	−51	+36

still be within the limits of 90 per cent of the population. For the T axis there is no significant difference between men and women in the mean change, but the postmeal variability is much larger in women. This means that very large postmeal changes in women may occur without indicating abnormality.

The Effect of Age. Our previous study on young men, though quite detailed, involved only 12 subjects. As in our present study of women, then, this means that the prediction of normal limits in a larger population must be somewhat questionable. However, the meal effect in the younger and the older men is closely similar and for most purposes it is probable that table 1 can be applied to both age ranges.

Changes in the QRS Complex and in the T Wave. There is evidence[9, 10] that, in general, an increasing R wave tends to decrease or invert the T wave so that an increasing left shift of the QRS axis is usually (i.e., in the absence of other changes) associated with an increasing shift of the T wave to the right. Since the general tendency after a meal is toward an increase in R (R_2 or Σ QRS) and a decrease in T, it might be suggested that the two changes are directly related. When, however, the individual values for the meal change in R_2 are compared with the corresponding changes in T_2 there is no significant correlation ($r = 0.098$). There was also no correlation between the changes of the QRS axis and those in the T axis. It must be concluded, then, that the change in T after the meal is not merely the result of a change in the QRS complex and it must be classified as nonphysiologic in the definitions of Ashman and Byer,[9] Ashman,[10] Wilson and Finch,[11] and Wilson and associates.[12] It would seem that the change in T produced by a meal is probably associated with a change in the ventricular gradient.

Cause of the Right Axis Deviation. The changes in the QRS axis observed after a meal may have some bearing on the causes of right axis deviation in general. In younger men[1] we found no significant change in the QRS axis after a meal. But, in older men, we find that a meal tends to produce a significant shift of the QRS axis to the right when the initial axis (before the meal) was below 50 degrees; with higher initial values there is essentially no change. These findings are difficult to explain on the basis of a simple change in position caused by filling of the stomach. In any case, we are forced to conclude that if a position change is involved here it seems to operate differently in older men with relatively vertical hearts than in other older men and in all younger men.

In all subjects, basal electrocardiograms were taken in 1948 and 1949, which made it possible to compare in subjects with extreme initial values in 1948 the repeat variability of the QRS axis (between years) with the trend after a meal (in 1949). This comparison was made on 10 subjects with a QRS axis below 26 degrees (mean 16.3 degrees $\pm$ 5.77) and on 9 subjects with a QRS axis above 70 degrees (mean 80.0 degrees $\pm$ 9.01). The mean postmeal change of the left axis group was $+18.9 \pm 14.66$ and that of the right axis group was -0.67 ± 4.12. The repeat variability of the left axis group, expressed as the standard deviation of the change between years, was $\pm$ 12.36; the comparable value for the right axis group was $\pm$ 4.47. It seems that a right QRS axis is less prone to variation than a left QRS axis, and this is true both with simple repetitions and with meal effects.

Precision of the Estimated Normal Limits. The main purpose of the present investigation was to obtain quantitative standards for the differentiation between normal and abnormal responses so as to characterize individual patients. The calculated limits of changes in 90 and in 98 per cent of a normal population are provided for this purpose, but our main experimental group of 42 men may seem rather small for comparison with individual patients. It is notable, however, that very similar results were obtained with women and with younger men. We believe, therefore, that the normal limits for the meal effect, as given in tables 1 and 3, are rather generally applicable.

Summary

1. In 42 normal men, 45 to 55 years, and in 12 normal women, aged 39 to 59 years, electrocardiograms were taken in the near basal

state and again shortly after a moderate meal. Leads I, II, III, V_1, V_2, and V_4 and CF_4 were recorded.

2. In a total of thirty-six electrocardiographic items measured and of thirty items statistically evaluated, there were statistically highly significant changes after the meal in twenty items. In several items the magnitude of the changes were comparatively small, but major consistent changes were increased heart rate, increased R amplitudes, decreased T waves, and a right QRS axis shift.

3. Normal standards for these meal changes, including predicted limits for 90 per cent and for 98 per cent of the population, are provided.

4. Differences between the women, and the younger men previously studied, and the middle-aged men were not statistically important.

5. For some items the pre-meal values influence the extent of the postmeal changes and normal standards adjusted to this fact are provided for six items.

6. The causes of the changes in the T waves and in the QRS axis are briefly discussed.

ACKNOWLEDGMENTS

We are grateful to the volunteers who acted as subjects. The electrocardiograms were taken with the assistance of Miss Erma v.O. Miller, Miss Laura Werner and Mrs. Nedra Foster. The records were measured by Mr. Heman Gursahaney who also made most of the statistical calculations.

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The Meal Test in Clinical Electrocardiography

By Ernst Simonson, M.D., and C. A. McKinlay, M.D.

The fact that an ordinary meal induces definite changes in the electrocardiogram suggested the possible utility of a meal test as a mild and convenient form of stress in clinical work. Comparison of normal persons and cardiac patients revealed frequent significant electrocardiographic differences in the response to a meal. This was especially notable in patients with proved or suspected coronary insufficiency. It appeared that the incidence of abnormal responses to the meal increased with the clinical degree of cardiac involvement. The response of the T wave was most frequently aberrant in patients.

Exercise,[1-4] anoxia,[2, 4-7] and drugs have been used recently as stresses to improve the electrocardiographic recognition of coronary insufficiency. Encouraging as the results are, certain disadvantages of these tests are apparent and have prevented their general acceptance in clinical routine examination.

In view of this situation we thought that the effect of a meal on the electrocardiogram held some promise as a clinical test procedure. Preliminary studies[10, 11] showed greater electrocardiographic changes after a meal in patients than in normal subjects.[12, 13] The stress produced by a moderate meal is mild and only repeats a situation which every person experiences in every-day life. The effect does not depend on the composition of the meal or its caloric content within fairly wide ordinary limits. Moreover, no significant trend in the changes was observed between 20 and 60 minutes after the meal.[12]

Method

Procedure. Electrocardiograms of 99 patients were taken before, and twenty to thirty minutes after, a meal of about 1,200 calories. In several patients additional electrocardiograms were taken. In all patients the three standard leads and CF_4 or V_4 were taken and in about half of the patients V_1, V_2 and V_6 were also recorded. In a few cases, unipolar limb leads were also used. The spots for the location of the chest electrodes were marked. The meal was given at noon (lunch) or in the morning (breakfast); in the first case the test was made at least three hours after a light breakfast of 200-300 calories, and in the latter case the patients came without breakfast to the laboratory. No smoking was allowed before or after the meal.

Method of Evaluation. The electrocardiographic items for each patient were compared with the normal standards obtained in 66 normal subjects (12 younger men, 42 older men, 12 older women).[12, 13]

Two criteria were used for differentiation between a normal and abnormal response of the electrocardiogram to a meal: the response was considered to be abnormal (1) when, according to accepted standards,[14] it was normal or borderline before the meal but abnormal after the meal; (2) when the changes exceeded the expectancy range for 98 per cent of the normal population.[13] In normal subjects it was found that the changes of CF_4 or V_4 were very similar,[13] so that the normal standards for V_4 may also be applied for CF_4.

Patients. All patients were ambulatory and in a state of apparent compensation at the time of the test. Most of them were between 40 and 60 years of age. About half of the patients (45) were members of a large experimental group of 500 subjects presently under study of this Laboratory.[15] In 29 patients, the electrocardiograms were the only abnormal (or borderline) findings of a thorough physiologic and clinical examination. Thus, the majority of our patients were in an incipient phase of cardiovascular degeneration, except a group of 23 patients with diagnosed coronary insufficiency.

The patients were grouped into six major categories: (I) Suspected coronary insufficiency (16 patients). (II) Coronary insufficiency (23 patients). (III) Arterial hypertension (21 patients). (IV) Patients with miscellaneous cardiac pathology other than coronary insufficiency or hypertension (6 patients). (V) Patients with borderline electrocardiogram, but clinically normal (10 patients). (VI)

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Patients with abnormal electrocardiogram, but clinically normal (23 patients).

All patients of Group I had episodes suggestive of coronary insufficiency, but the electrocardiogram (before meal) was normal (11 patients) or borderline (5 patients). Two of these patients had arterial hypertension.

Group II consisted of patients with definite coronary insufficiency, including 9 patients with healed myocardial infarct and little or no complaints at the time of the test. The electrocardiograms of all 23 patients were abnormal, mostly showing nonspecific T and S-T segment changes. Two of these patients had left bundle branch block.

2 cases with arrhythmia (multiple premature ventricular beats) and one case with left bundle branch block.

Results

Individual Examples of Abnormal Changes. The most frequently observed abnormal change (tables 1 to 3) was a decrease (or inversion) of the T wave, mostly in Lead I or II. The T-wave change is, of course, most impressive when a formerly positive T wave becomes flat, diphasic or inverted. Examples of a change of

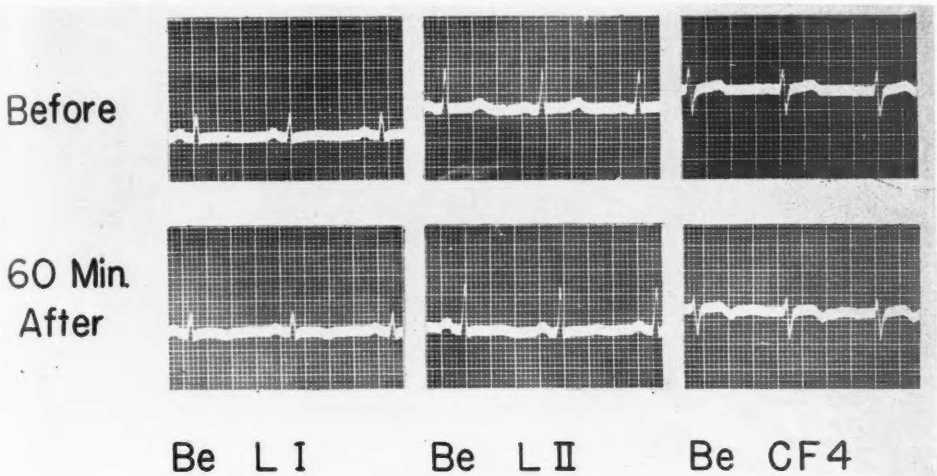

Fig. 1.—In a patient (woman, age 59 years) with suspected coronary insufficiency, a flat T_1 becomes inverted after the meal, the positive T_2 becomes subnormally low, and the normal T in CF_4 diphasic, mainly inverted.

In Group III (total 21), the electrocardiogram was normal in 6, borderline in 2, and abnormal in 13 patients. Left ventricular strain pattern was present in 6 patients. One patient had left bundle branch block. As to the degree of hypertension, 5 were classified as mild, 11 as moderate, and 5 as severe.

Group IV was small (6 patients) and heterogeneous, including one case of aortic aneurism, one of aortic insufficiency and one of cardiac neurosis.

Out of 10 clinically normal patients with borderline electrocardiograms (Group V), 6 had a Q_3 wave preceded by a tiny R and followed by a larger R′. However, in 5 of them there was no abnormal Q wave in Lead V_F, while one patient had a borderline Q wave in this lead.

Group VI included 8 cases with left ventricular strain pattern; 4 cases with A-V block first degree; 7 cases with nonspecific changes in the T wave;

the T wave in the direction toward greater abnormality are shown in figures 1, 2 and 4, Patient Si. It is evident, that a suspicion of myocardial involvement because of the low T_1 in Patient Be (fig. 1) was strengthened by the result of the meal test.

Figure 3 shows major changes of the T wave in CF_2 and CF_4 toward normality associated with an S-T depression in Lead II, and an exaggerated increase of the heart rate. The patient experienced marked discomfort after the meal, which was relieved by nitroglycerin, together with disappearance of the $S\text{-}T_2$ depression and reduction of the heart rate to normal.

An increase of an abnormal Q wave in Lead

CF_4 associated with a late dip of the T wave, is shown in figure 4 (Patient Hi). An increase of the Q wave is rare, and was observed only in patients with coronary insufficiency.

Incidence of Abnormal Responses in Various Clinical Groups. The incidence of abnormal responses was surprisingly high; 75 out of 99 patients showed abnormal changes of one or another type. Table 1 shows the incidence of the most frequently observed types of abnormal response in the six clinical groups. Changes of the T wave, of the S-T segment, and of the heart rate are the most important electrocardiographic items for investigation of meal effects. The number of items listed is cumulative; most patients showed an abnormal response in more than one item.

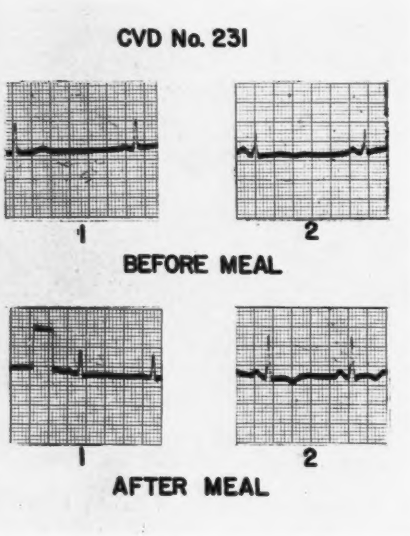

FIG. 2.—In Patient 231 (man, age 50 years, mild hypertension) a normal (though somewhat low) T_1 becomes almost flat and the subnormal T_2 inverted, associated with an S-T depression. There is also an increase of the heart rate of about borderline significance.

As a whole, Group II (coronary insufficiency) represents a more advanced phase of myocardial involvement than Group I (suspected coronary insufficiency). The incidence of abnormal responses for the whole group as well as the number of abnormal items per patient having an abnormal response (table 1, last column) is somewhat higher in Group II than in Group I. The number of abnormal responses per patient was substantially lower in the patients of Groups V and VI, who were probably in an initial phase of myocardial involvement, since they were clinically normal. Thus, the results show a trend towards greater incidence of abnormal responses with the degree of myocardial involvement. Also, comparison of patients of Group III with normal and abnormal electrocardiogram (table 2) shows a similar trend.

In the limb leads a decrease of the T wave (change towards negativity) was much more frequent than an increase (table 1), while in V_4 (or CF_4) increase and decrease are about equally frequent. The incidence of increases was greatest in Group II. An abnormal T-axis shift occurred more frequently in patients with arterial hypertension (Group III) than in any other group.

Association of Various Abnormal Responses. Table 2 shows the number of patients with abnormal changes of the T wave, heart rate, and S-T segment, and the association of such changes with one another and with other (not classified) abnormal responses. No breakdown is made as to the direction of change (increase or decrease); the figures in table 2 refer to the number of patients with any type of abnormal response in the given item.

Of 75 patients with abnormal responses to a meal, 54 had abnormal T-wave changes, and in about half of this number the T-wave change was the only abnormal electrocardiographic item. Abnormal T-wave changes were most frequently associated with other abnormal responses in patients with coronary insufficiency (Group II). Association of T-wave changes was more common in patients of Group III with abnormal electrocardiogram than in patients of the same group with normal electrocardiogram.

The change of the heart rate was abnormal in 38 patients, and associated with other abnormal changes in 22 patients. It is of interest that no isolated S-T changes were observed.

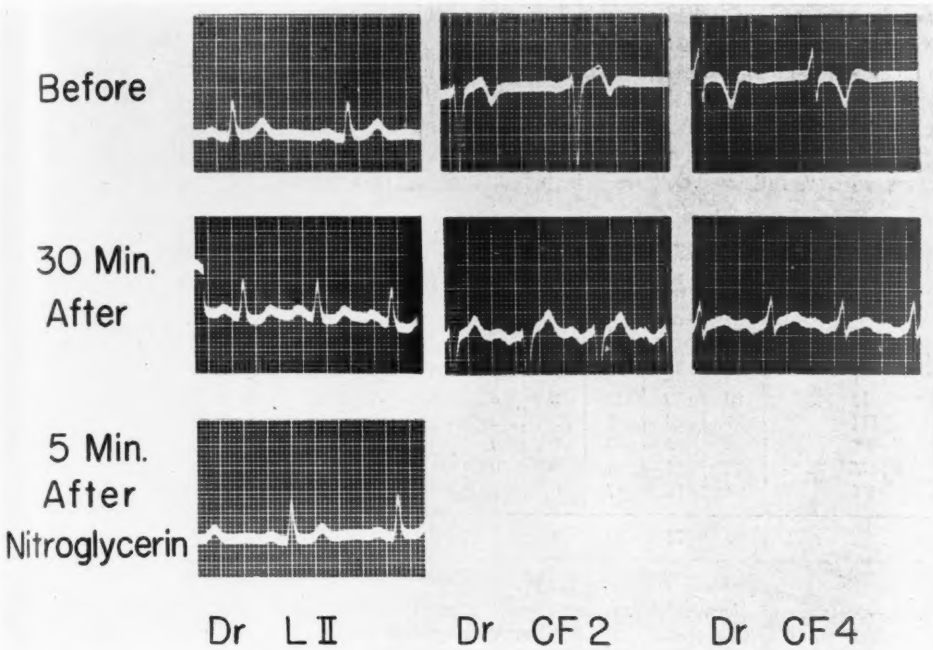

FIG. 3.—Changes towards normality in T-CF_2 and T-CF_4 after meal in a patient (man, 59 years) with coronary insufficiency and distress after the meal, while an S-T depression appears in Lead II. The increase of the heart rate is exaggerated. The changes of Lead II disappear after administration of nitroglycerin.

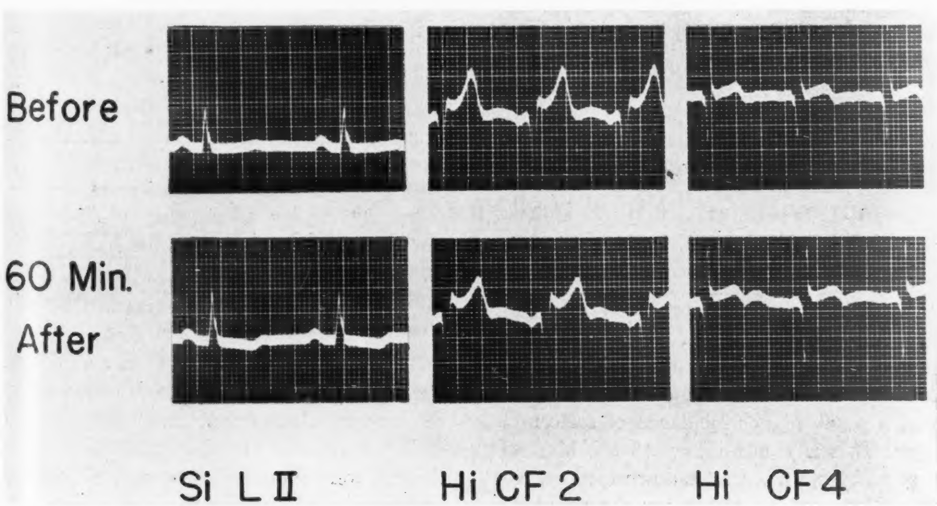

FIG. 4.—Increase of the Q wave in CF_4, associated with a slight late negative dip of the T wave after meal in Patient Hi (man, 54 years) with coronary insufficiency (history of anterior wall infarct). Inversion of a low T_2 in Patient Si with coronary insufficiency.

Incidence of Abnormal Responses in Various Electrocardiographic Patterns. Table 3 shows the incidence of abnormal electrocardiographic changes in groups classified according to the electrocardiographic pattern before meal. In 18 patients with borderline electrocardiogram, 6 cases with "suspicious Q_3" were included, high. In 9 patients with healed infarct and little or no complaints the incidence of abnormal responses, especially depression of T_1, T_2 or Σ T, is comparatively low. The incidence of abnormal responses, especially T-wave changes, was definitely higher in left ventricular preponderance (LVP) of the ST_1T_1 type[14] or

TABLE 1.—*Incidence of Abnormal Electrocardiographic Changes after Meal in Six Clinical Groups*

Clinical Category	No. Pat.	No. Pat. with Abn. Resp.	T_1, T_2, Σ T		T-CF_4 T-V_4		T Axis	S-T Depr.	Heart Rate			Other Changes	Abn. Items per Pat. with Abn. Resp.
			Decr.	Incr.	Decr.	Incr.			Decr.	No Change	Incr.		
I	16	12	9	0	1	0	0	3	2	3	1	2	1.75
II	23	19	11	2	3	5	0	3	5	3	2	4	1.89
III	21	16	8	2	2	1	5	3	2	2	4	1	1.88
IV	6	5	3	0	0	0	1	0	1	0	2	1	1.60
V	10	5	1	0	0	1	0	2	1	0	3	0	1.60
VI	23	18	7	0	1	2	3	0	2	1	4	6	1.45
Total..............	99	75	39	4	7	9	9	11	13	9	16	14	—

TABLE 2.—*Incidence of Abnormal Electrocardiographic Changes after Meal and Association of Changes in Several Electrocardiographic Items*

Clinical Category	No. Pat.	No. Pat. with Abn. Resp.	T wave					Heart Rate				S-T Alone	Other Alone
			Total	Alone	Assoc. with			Total	Alone	Assoc. with			
					S-T	H. Rate	Other			S-T	Other		
I	16	12	9	6	1	3	2	6	2	2	1	0	0
II	23	19	15	6	4	6	3	10	5	3	3	0	1
III	21	16	13	6	3	5	3	8	3	2	1	0	1
IV	6	5	4	3	0	1	1	3	2	0	1	0	0
V	10	5	2	1	1	1	0	4	2	2	0	0	0
VI	23	18	11	7	0	2	2	7	2	0	5	0	3
Total................	99	75	54	29	9	18	11	38	16	9	11	0	5
III, Normal ECG	8	5	3	3	0	0	0	2	2	0	0	0	0
III, Abn. ECG	13	11	10	3	3	5	3	6	1	2	1	0	1

i.e., a downward deflection preceded by a tiny R, and followed by a larger R′. In only one of these cases was a possibly abnormal Q noted in Lead V_F. The 12 remaining borderline cases showed a much higher incidence of abnormal changes. This is confirmatory to the impression, gained from V_F, that a downward deflection in Lead III preceded by a tiny R is probably not abnormal. Also, the incidence of abnormal responses in 25 patients with nonspecific S-T segment or T changes is very high voltage type[16] than it was in LVP of the S_2 type.

Abnormal changes of the QRS complex were observed only in 7 cases which contrasts with the large number of abnormal T-wave changes. This discrepancy implies that the T-wave changes were primary[17, 18] (nonphysiologic) and associated with changes of the ventricular gradient. This was also true for the T-wave changes after a meal in normal people.[12, 13]

Patients with A-V Block and Bundle Branch

Block. Our group included 5 cases with a P-R interval exceeding 0.22 second. Table 4 shows that, with the exception of one case, the P-R intervals were substantially shorter after the meal, so that in 3 patients the P-R interval was within normal limits after the meal. Although the group is small, the uniformity of response should not be ignored.

by means of the meal test appears to be high, but this, of course, will depend on the selection of the group and the definition of "suspected coronary insufficiency," which is arbitrary to a high degree.

In 2 instances the meal test revealed more generalized involvement in patients with minor abnormalities in the electrocardiogram before

TABLE 3.—*Incidence of Abnormal Electrocardiographic Changes after Meal in Several Groups Classified According to Electrocardiographic Pattern before Meal*

ECG Categ.	No. Pat.	Pat. Abn. Resp.	Abnormal Changes									
			$T_1, T_2, \Sigma T$		$T\text{-}CF_4$ $T\text{-}V_4$		T Axis	S-T Depr.	Heart Rate			Other
			Decr.	Incr.	Decr.	Incr.			Decr.	No Change	Incr.	
Normal	18	12	6	0	4	0	0	2	0	3	1	2
Borderline	18	11	5	0	0	1	0	2	3	1	4	2
B.L. without susp. Q_3	11	10	5	0	0	1	0	2	2	0	4	2
Non-spec. S-T or T	25	22	13	3	5	4	1	3	3	1	3	2
Healed Infarct	9	6	2	1	0	2	0	0	2	2	0	0
LVP; S_2 Type	10	6	2	0	0	1	0	0	3	2	3	0
LVP; ST_1T_1 Type	7	6	4	1	1	1	3	3	0	1	2	1

The response of 4 patients with bundle branch block was less uniform, which is not surprising, since left bundle branch block may obscure even the occurrence of infarct. Abnormal changes were observed in 3 patients, one of which is demonstrated in figure 5.

Conversion of Previously Normal to Abnormal Electrocardiogram. One of the main purposes of the use of stress situations for diagnosis is the detection of latent involvement. The conversion of a normal or borderline electrocardiogram to an abnormal electrocardiogram after the meal could be regarded as a positive test result in that sense. Table 5 shows the number of patients with normal and borderline electrocardiograms before meal, which became abnormal after the meal. The 5 patients of Group V with "suspicious" Q_3, but probably within normal limits, were not included. The total incidence of abnormal electrocardiograms after the meal is high (about 50 per cent), but mainly on account of patients with suspected coronary insufficiency (Group I). Therefore, the chance of discovering latent changes in patients with suspected coronary insufficiency

TABLE 4.—*Electrocardiographic Changes after Meal in Patients with Partial A-V Block*

Patient No.	Sex	Age	Group	P-R interval (sec.)		Other abnormal Changes
				Before	After meal	
265	M	52	IV	0.24	0.20	low T_1, diph. T_2
495	M	47	VI	0.23	0.19	decreased heart rate
318	M	54	VI	0.29	0.25	excessive incr. heart rate
496	M	47	VI	0.25	0.20	None
477	M	47	VI	0.23	0.23	None

a meal. In patient 265 (fig. 6), the P-R interval was prolonged before the meal; since the prolongation is slight, the importance is questionable in the absence of other abnormalities. After the meal, the P-R interval was shortened (cf. table 5), but this was associated with $S\text{-}T_2$ depression and a diphasic, mainly negative T_2.

Corroboration of Tentative Interpretation of Basal Electrocardiogram. The meal test also appears to be valuable when a tentative interpretation can be made more definite. The elec-

trocardiogram of Patient 282 (fig. 7) was interpreted as probable left ventricular preponderance, because of somewhat high voltage of the R wave in V_F, and that of Patient Mag (fig. 6) showed left ventricular strain pattern pattern, due to the vertical position of the heart.

Reproduction of Abnormal Characteristics. In 2 patients a transient T inversion was found in Lead I and CF_4, probably due to an episode

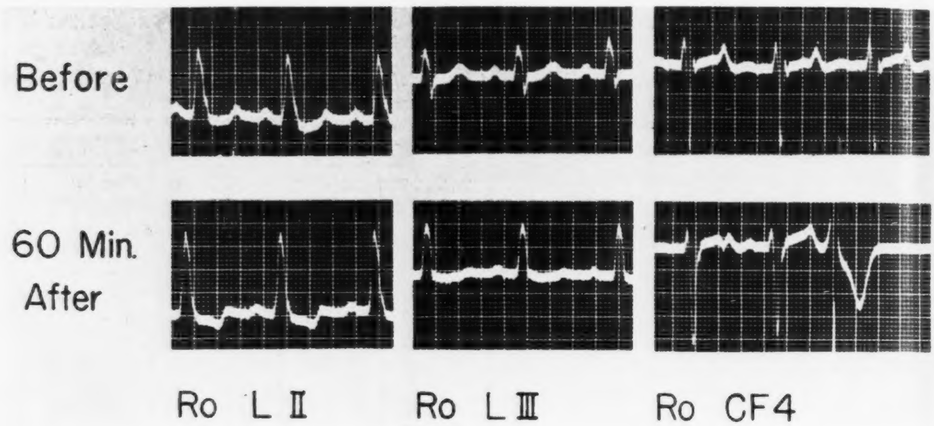

FIG. 5.—Abnormal changes after meal (T_2 diphasic, mainly negative instead of positive; flattening of T_3; disappearance of S_3; replacing of R'S' in CF_4 by a slurring of the upstroke of S near the baseline) in a patient with left bundle branch block and coronary insufficiency.

TABLE 5.—*Patients with Normal or Borderline Electrocardiogram before Meal and Abnormal Electrocardiogram after Meal*

Total Number Pat.	ECG before meal	Group	ECG after Meal: Number of Pat. with Abn. ECG	Low, diph. or neg. T_1, T_2	Low, diph. or neg. T-CF_4 T-V_4	S-T depression	Other Changes
11	normal	I	7	6	2	1	0
6	normal	III	1	1	0	0	0
1	normal	IV	1	1	0	0	0
5	borderline	I	4	3	0	1	0
2	borderline	III	1	1	0	0	0
1	borderline	IV	0	0	0	0	0
5	borderline	V	2	1	0	2	0
Total 18	normal		9	8	2	1	0
Total 13	borderline		7	5	0	3	0

in V_6. The standard leads of both patients did not show a left ventricular strain pattern due to the vertical position of the heart, as interpreted from the unipolar limb leads (not shown in fig. 6). After the meal, a definite left ventricular strain pattern appeared in V_F of Patient 282 (fig. 7), while the standard leads in both patients showed a right ventricular strain of coronary insufficiency. The meal test was made after the T wave had become normal and reproduced an earlier phase of recovery with abnormal T waves.

In 2 patients, after the meal a pulsus bigeminus reappeared, which was found on former and later occasions before the meal but was absent on the day of the meal test. The appearance

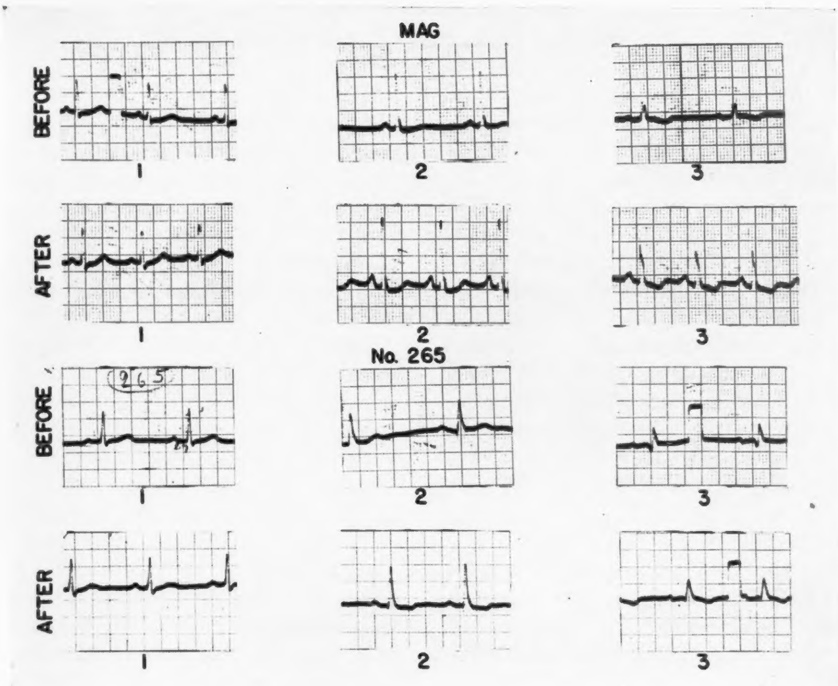

FIG. 6.—Marked S-T_2 and S-T_3 depression after meal in a patient (man, 39 years, severe hypertension) with left ventricular strain in a vertical heart (diagnosed by means of the chest leads, not shown in this figure). T_2 and T_3 inversion after meal in Patient 265 (man, 51 years of age) with aortic aneurism on luetic basis. Three standard leads.

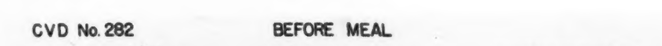

FIG. 7.—The electrocardiogram before meal shows high voltage in Lead V_F, suspicious of left ventricular preponderance in a vertical heart. After meal, V_F shows left ventricular strain pattern, which produces a T_3 inversion due to the vertical position. (Man, 51 years, no abnormal clinical findings.) Three standard leads and 3 unipolar limb leads. Standardization in V_R, V_L and V_F. 1mv = 15 mm.

of the pulsus bigeminus was associated with abnormal T waves in Lead I or CF_4.

Discussion

Possible Mechanism of Meal Effects. The stress produced by eating a meal is very small in terms of oxygen transport, compared to the mildest physical exercise. It was assumed,[12, 13] therefore, that the changes of the electrocardiogram after a meal in normal people cannot be due to the increase of load in terms of oxygen consumption, and the same is true for most cardiac patients. It is also unlikely that the changes after meal are due to myocardial anoxia in normal people, though this might be different in some patients. In 2 patients who experienced discomfort after the meal a pronounced S-T depression, reversed by nitroglycerin, was interpreted as indicative of transient coronary insufficiency. In any event, the mechanism of meal effects must be different from that involved in exercise or anoxia tests. The high incidence of abnormal electrocardiographic responses after a meal in various groups of cardiac patients shows that interference with the normal mechanism of mediation of cardiac meal effects is so common in most types of myocardial involvement that it may be used for diagnostic purposes.

Significance of Heart Rate and T-wave Changes. Abnormal changes of the heart rate are, according to incidence, the second most important item, but they are subject to emotional interference. Furthermore, noncardiac pathology may produce an abnormal response of the heart rate, though actual information is not yet available.

In women a decrease of the heart rate must exceed 5 beats per minute to be called abnormal, but a decrease of such magnitude was not observed in our group.

Of the various abnormal changes, the T-wave changes are the most important in regard to incidence and significance. The results of follow-up observations in 16 patients over a period from one to three years after the meal test seem to support the significance of T-wave changes. Eight patients with suspected or definite coronary insufficiency, who had abnormal changes in the T wave after a meal, continued to have angina pectoris or showed electrocardiographic evidence of progressive myocardial involvement, and 2 had subsequent coronary thrombosis. Of 4 patients of these groups who had a normal response or an abnormal response only of the heart rate, 3 showed no further development. We wish to emphasize, however, that the material is too small for any definite conclusion.

The Meal Test and Other Stress Tests in Electrocardiography. According to Burchell and associates,[7] a positive anoxia test may be expected in about 50 per cent of patients with coronary sclerosis. It seems surprising that the incidence of positive meal tests exceeds the incidence of positive anoxia tests, although induced anoxia is a more severe stress situation than the intake of moderate meals. However, the criteria for the induced anoxia test are qualitative rather than quantitative. No normal standard material is available for the anoxia test comparable to that for the meal test.[13] It seems safe to expect that the incidence of positive results would be higher for the anoxia test if such material were available for quantitative comparison of patients. Also, the necessary selection of patients for the anoxia tests is bound to decrease the incidence of positive results. Since the physiologic basis of the meal test is different from that of exercise or anoxia tests, they are supplementary.

Problems of interpretation and application. It is suggested that the meal test be used in clinical routine but with caution in interpretation. In general, it may be assumed that an existing suspicion of myocardial involvement will be strengthened by a positive meal test. The validity of using changes of *normal* subjects as the basis for predictions in *patients* may be questionable. It seems reasonably safe, however, to use the expected normal limits of changes, when the change occurring after the meal is in the direction of greater abnormality. We are on less safe ground with changes in the direction towards greater normality. However, a gross change towards normality after the meal, for instance a reversal of the direction of abnormal inverted T waves, was considered as abnormal response. In a similar way, reversal in the direction of abnormal T

waves after exercise is also interpreted as abnormal response.[19] However, such interpretation might not be correct for minor changes towards normality, but this was rare in our group (2 cases). Of the two criteria used, the first (conversion of normal to abnormal) revealed abnormal responses in 30 out of 75 cases. Both criteria do not exclude one another, and the comparison with the 98 per cent range limits (second criterion) was used in every case. Since the normal changes in several items are comparatively large, the second criterion was as valuable to exclude as to prove an abnormal response.

Our group of patients is preselected in regard to age distribution as well as to clinical involvement. The most important involvement (suspected or manifest) in our group is coronary insufficiency, and the interpretation of our results depends naturally on the composition of our group. It is quite possible that the meal might produce other patterns of response in other types of myocardial involvement, or a different incidence of abnormal responses in the same groups, dependent on chance distribution and definition of clinical groups.

Summary

1. The effect of an ordinary meal on the electrocardiogram of 99 cardiac patients was compared to the effect in normal people. The patients were subdivided into six clinical groups: (I) suspected coronary insufficiency; (II) coronary insufficiency; (III) arterial hypertension; (IV) miscellaneous myocardial involvement; (V) borderline electrocardiogram, clinically normal; (VI) abnormal electrocardiogram, clinically normal.

2. The incidence of abnormal responses was high for all groups (75 per cent of the total group), but there was a tendency toward appearance of multiple abnormal changes with increasing myocardial involvement.

3. Abnormal changes were most frequently observed in the T wave, especially a decrease (or inversion) of T_1, T_2, T-V_4 or Σ T, but also abnormal increases of the T wave were observed.

4. The next important item in regard to the incidence was the change of the heart rate, either an exaggerated increase, or failure to increase the heart rate, or decrease of the heart rate after meal.

5. An abnormal depression of the S-T segment was fairly common, but it was always associated with other abnormal changes, chiefly of the T wave. It is assumed that a marked S-T depression in 2 patients was associated with an attack of transient coronary insufficiency, precipitated by the meal.

6. Problems of applicability, standardization and physiologic background are discussed.

Acknowledgments

We wish to thank the patients for their cooperation. The electrocardiograms were taken with the assistance of Miss E. v. O. Miller, Miss Laura Werner, Mrs. Nedra Foster and Miss Margaret Doran.

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The Effect of Meals on the Electrocardiogram and the Ballistocardiogram in Patients with Angina Pectoris

By Bernard Berman, M.D., John R. Braunstein, M.D., and Johnson McGuire, M.D.

The effect of meals on the electrocardiogram and the ballistocardiogram was studied in 59 patients with angina of effort. Approximately one-fourth of the group showed a 0.5 to 1.0 mm. depression of the S-T segment, while the normal controls did not show this change. Premature ventricular contractions and inversion of the T wave were found more frequently in patients with angina following meals than in normal individuals. The patients with angina were unable to increase the cardiac output significantly following meals as compared to normal individuals. It is suggested that these findings may prove to be of value in evaluating cardiac function in patients with angina.

IT HAS BEEN shown that changes appear in the electrocardiogram of normal individuals following the ingestion of moderate meals.[1–3] The most important effect of the meals in normal subjects is a decrease in the voltage of the T wave, and, in addition, an increased heart rate, decreased duration of mechanical systole, decreased Q-T interval, and an increased QRS amplitude.[2]

Electrocardiographic tracings of thirty-two patients with angina of effort, from the Out-Patient Department of the Cincinnati General Hospital, made thirty minutes following meals showed a 0.5 to 0.75 mm. depression of the RS-T segment, and the development of, or an increase in, the existing concavity of the RS-T segment as compared with tracings made before ingestion of meals.[3] These findings may well be in accord with those of Moia and

Table 1.—*Average Difference in Electrocardiographic Findings in Patients with Angina and Control Subjects, before Meals and Thirty Minutes following Meals*

	Control Subjects	Patients with Angina
Average increase in heart rate/min.	5.02	7.1
Averate T-wave changes:		
Lead I (mv.)	−.47	−.55
Lead II (mv.)	−.31	−.41
Lead III (mv.)	−.32	−.47
Lead V_1	−.02	−.02
Lead V_2	−.05	−.06
Lead V_3	−.06	−.07
Lead V_4	−.05	−.06
Lead V_5	−.05	−.05
Lead V_6	−.04	−.03
RS-T segment	No significant change	Significant change
P-wave duration	No significant change	No significant change
P-R interval	No significant change	No significant change
P-wave amplitude	No significant change	No significant change
Q wave	No significant change	No significant change

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This study was made possible by a grant in aid from the Life Insurance Medical Research fund.

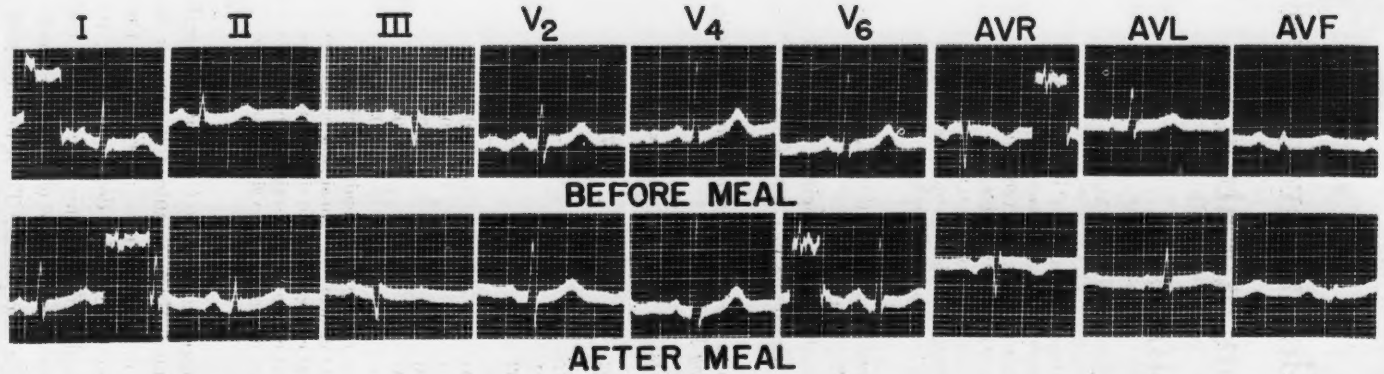

FIG. 1—(Normal subject) Electrocardiograms, made before and thirty minutes following a meal, of a normal 58 year old woman, a hospital attendant. The most important effect is a decrease in the voltage of the T waves.

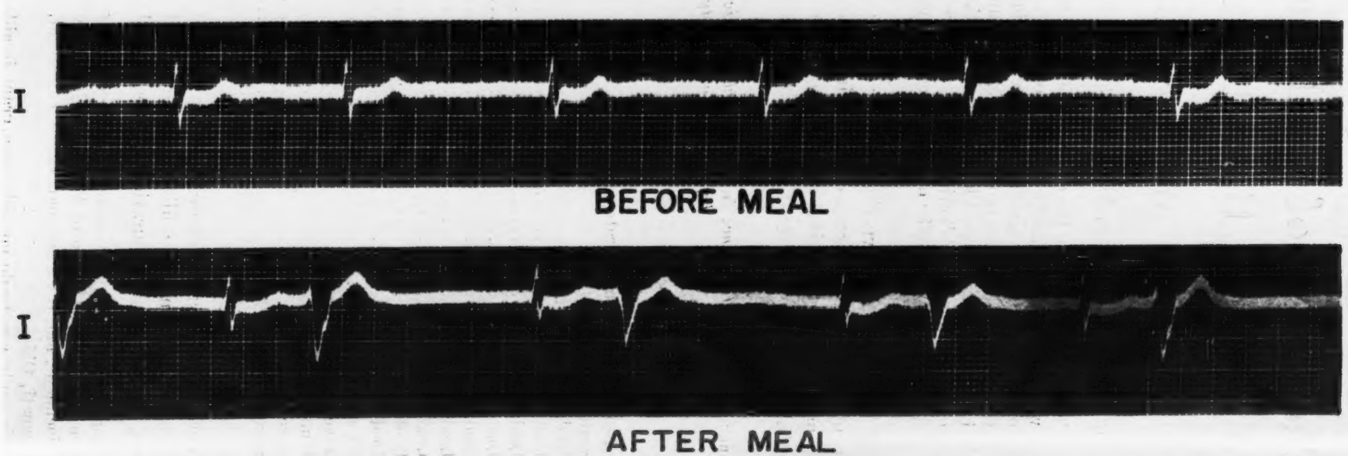

FIG. 2.—(Patient with angina) Lead I of electrocardiogram, made before and thirty minutes following a meal, showing the develop-

Battle,[4] who reported alterations characteristic of myocardial ischemia in the electrocardiograms made after meals in 27.2 per cent of the patients suffering with angina, although the criteria used in diagnosing myocardial ischemia were not stated.

In order to study the effect of a standard meal on both the electrocardiogram and cardiac output in patients with angina, ballistocardiograms were also made following meals.

coronary arteriosclerosis, and a large number of these had evidence of previous myocardial infarctions. One patient had rheumatic heart disease, and one patient had syphilitic heart disease. Their ages ranged from 48 to 70 years.

Electrocardiographic Results

Table 1 shows the average difference in electrocardiographic findings in the patients with angina and the control subjects, before meals and thirty minutes following meals.

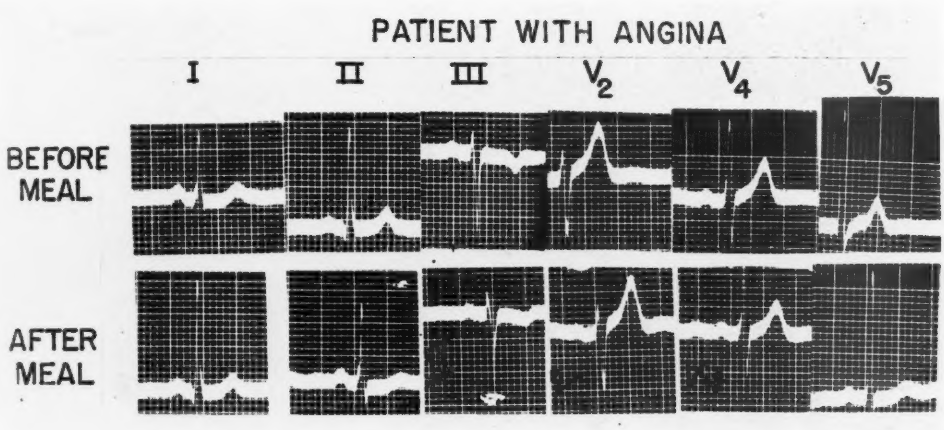

Fig. 3.—(Patient with angina) Electrocardiograms made before and thirty minutes following a meal. The patient, a 50 year old white physician, had mild angina. There is depression of the RS-T segment in Lead II following the meal. The patient had received no medication.

Method

Fifty-nine patients suffering with angina of effort, fifty of whom were patients of the Out-Patient Department and the Medical Service of the Cincinnati General Hospital, were fed ninety-one standard mixed meals, consisting of 90 grams carbohydrate, 40 grams protein, and 40 grams fat. Warm drinks were given with each meal. Twenty normal controls in the same age group, consisting mainly of employees at the Cincinnati General Hospital, and ranging in age from 50 to 70 years, were given similar meals. Electrocardiograms and ballistocardiograms were made in both groups before meals and thirty minutes following the meals; the subjects rested fifteen minutes before ballistocardiograms were made. The electrocardiograms included limb leads, six standard unipolar chest leads, and augmented unipolar extremity leads. Only patients who gave a typical history of precordial pain on exertion, relieved by rest or nitroglycerin, were included in this study. Fifty-seven patients had

Approximately 25 per cent of the patients with angina showed a 0.5- to 1.0-mm. depression of the RS-T segment, and the development of, or increase in, existing concavity of the RS-T segment. In some of the patients the segment shift occurred in one or more of the limb leads, while in others the change was apparent only in one or more of the V leads. No member of the control group showed a shift of the RS-T segment. In 10 patients extrasystoles occurred, while this change was not noted in the controls. In 20 per cent of the patients with angina, inversion of the T wave appeared following meals in one or more of the leads. One of the members of the control group showed T-wave inversion following the meal. This change was found in Lead III. In 2 patients with angina, amplitude of the

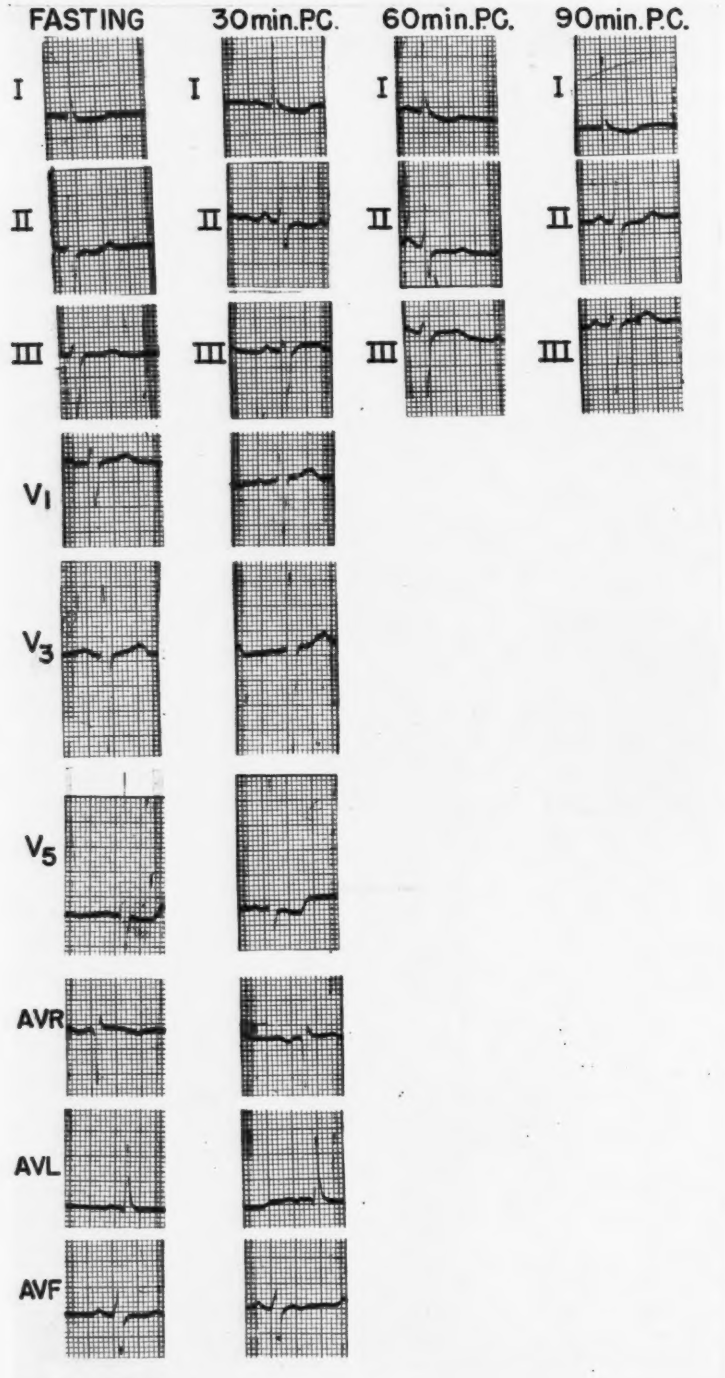

FIG. 4.—(Patient with angina) Electrocardiograms made while the subject was fasting and thirty minutes, sixty minutes, and ninety minutes following a meal. This patient was a 50 year old Negro woman with hypertensive, arteriosclerotic heart disease, and angina. The electrocardiogram did not demonstrate return to the fasting state until sixty to ninety minutes after the meal.

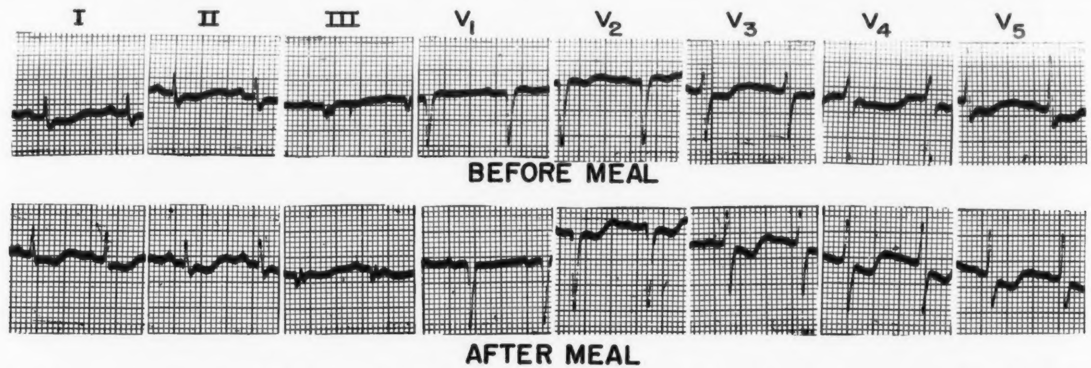

FIG. 5.—Electrocardiograms, made before and after a meal on patient with angina, showing depression of the RS-T segments in Leads I and II and in the V leads, with increase in the pre-existing concavity of the RS-T segment. The patient was receiving digitalis therapy.

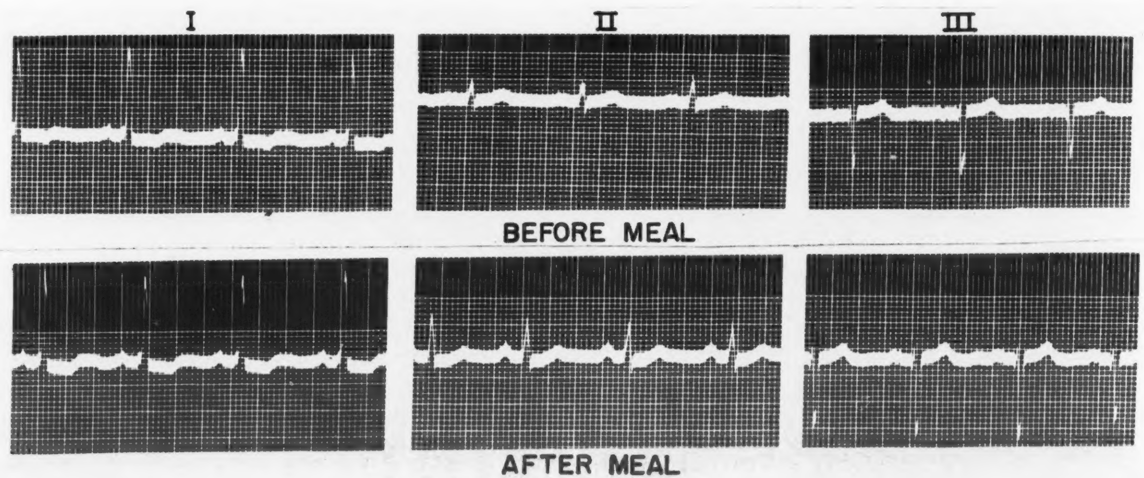

FIG. 6.—Electrocardiograms of a patient with angina made before and following a meal. Lead II shows the depression of the RS-T segment following the meal.

T wave increased following the meal. Both of the patients showing increased voltage of T waves following meals had severe angina, decreased amplitude in the ballistocardiogram. Eleven patients with angina showed no apparent change in amplitude following meals.

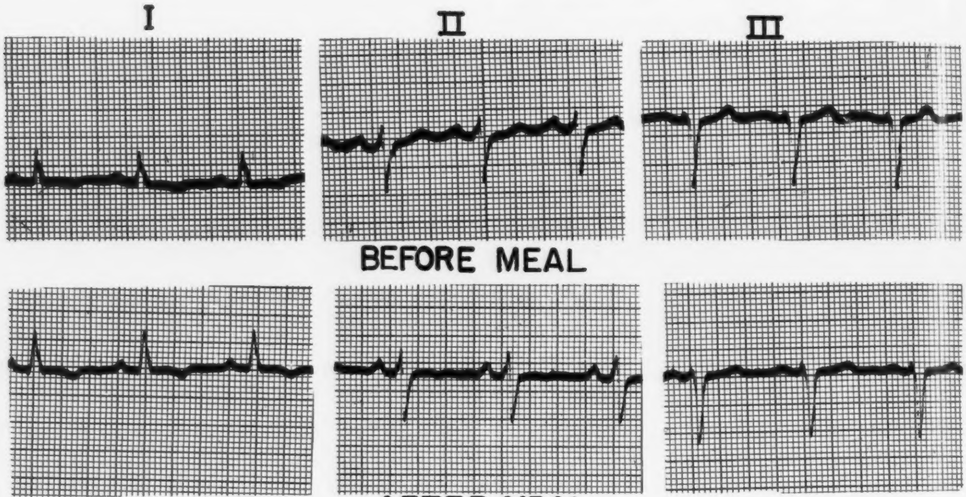

Fig. 7.—Electrocardiograms of a patient with angina made before and thirty minutes following a meal. The T wave in Lead II has become diphasic.

and one patient died while asleep. Five of the patients with angina complained of chest pain following the meal, and these patients showed no distinct alterations in the electrocardiogram as compared to other members of the group.

Figure 1 shows electrocardiograms of a normal subject made before and thirty minutes following a meal. Figures 2 to 7 show electrocardiograms of patients with angina made before and after meals.

Ballistocardiographic Results

In 23 patients, ballistocardiographs were made before and following meals. Five patients with angina, not in congestive failure, in whom the tracing conformed to a normal pattern, showed the ballistocardiographic changes following meals which are summarized in table 2.

In 18 patients with angina, the ballistocardiograms were distinctly abnormal in pattern, and since the formulas for abnormal patterns have not been derived the cardiac output could not be calculated. Of these 18 patients, however, only 4 showed a slight increase in amplitude following meals, while 3 patients had

Table 2.—*Ballistocardiographic Changes before and following Meals in Patients with Angina, not in Congestive Failure, and in Control Subjects.*

Before Meals (Liters/Min) Angina (not in congestive failure)	30 Minutes Following Meals (Liters/Min.)
8.4	8.2
5.7	5.1
5.2	4.8
6.9	7.0
6.7	6.5
32.9	31.6 (−4%)
Controls	
5.8	6.6
4.1	7.7
7.1	6.5
5.8	6.1
6.0	8.4
4.8	6.6
34.6	42.9 (+24%)

Ballistocardiograms, made before and thirty minutes following a meal, of a normal individual and a patient with severe angina are shown in figures 8 and 9 respectively.

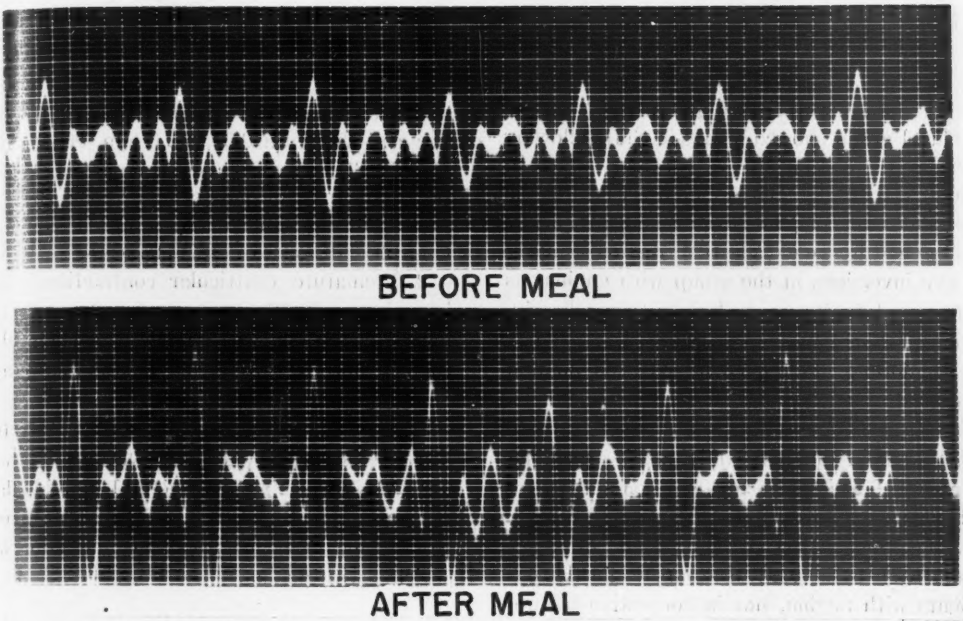

FIG. 8.—(Normal subject) Ballistocardiograms, made before and thirty minutes following a meal, showing normal response to meal with increase in cardiac output. The patient, C. G., was a nurse 52 years of age. She had no organic heart disease.

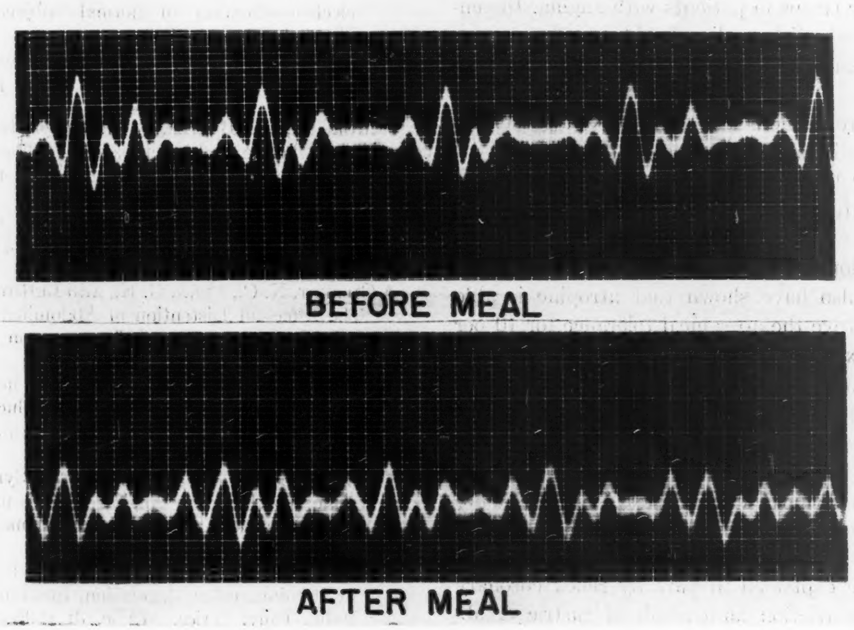

FIG. 9.—(Patient with angina) Ballistocardiograms, made before and thirty minutes following a meal, showing decrease in cardiac output. The patient was a 53 year old white machinist with severe angina. He died while asleep.

Discussion

It is of interest that no member of the control group showed an RS-T shift following the meals, in contrast to the appearance of depressed RS-T segments in 25 per cent of the patients with angina. The greater frequency of premature ventricular contractions and T-wave inversions in the group with angina, as compared to the control group, may be significant.

In normal individuals it has been pointed out that the ingestion of food results in an increased cardiac output, varying from 0.5 to 2.0 liters in different individuals, depending upon such factors as size and composition of the meals.[5] In our series the average cardiac output following meals increased 1.4 liters (24 per cent) in the control group, while the patients with angina, not in congestive failure, failed to show a significant change. The inability of the patients with angina to increase the cardiac output significantly following meals seems striking enough to suggest that this finding may be utilized in attempting to evaluate cardiac status in patients with angina. In general, the ballistocardiographic results were more informative than the electrocardiographic findings.

Many authors have pointed out the extracardiac influences exerted on the coronary arteries,[6-12] and von Bergman[8] and Gilbert and associates[6, 7] have shown that coronary flow may be reduced by distention of the stomach or abdominal cavity. Gilbert, Fenn, and Le Roy[6] also have shown that atropine is able to improve the after-meal tolerance for 10 per cent oxygen in patients with angina. Studies are now in progress to determine the influence of atropine on the after-meal electrocardiogram and ballistocardiogram in patients with angina.[13] Preliminary work tends to substantiate Gilbert's view that increased incidence of anginal pain following meals need not be explained solely by increased cardiac work, but may well be explained in part by reflex coronary vasoconstriction as a result of gastric or abdominal distention.[13]

Summary

1. In 59 patients with angina of effort, 25 per cent showed a 0.5- to 1.0-mm. depression of the RS-T segment, and the development of, or an increase in, the existing concavity of the RS-T segment, following meals. Normal controls did not show this change.

2. Premature ventricular contractions and inversion of the T wave were found more frequently in patients with angina following meals than in normal individuals. This finding may be significant.

3. The patients with angina were unable to increase the cardiac output significantly following meals as compared to normal individuals. It is suggested that this finding may prove to be of value in evaluating cardiac function in patients with angina.

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The Variability of Cardiac Output Estimations Made with the High-Frequency Undamped Balistocardiograph

By Robert M. Paine, M.D., and Nathan W. Shock, Ph.D.

Recordings of the ballistocardiogram were made on successive days in a group of subjects free from clinical signs of heart disease. The effects of ambulation and meals on the recordings were evaluated. A small but measurable increase in cardiac index following meals was observed. Significant individual differences were found. In order to obtain comparable ballistocardiographic records, it is important for the patient to fast for four to five hours preceding the measurements. However, familiarity with the procedure and prior bed rest are not essential. Only one set of calculations by one observer is required.

EVIDENCE has been presented by Starr[1] that preclinical coronary disease can be detected by means of the ballistocardiograph. In a series of 90 persons selected as normal subjects for ballistocardiographic study, a number were found to manifest frank coronary artery disease in the course of a ten-year followup. Of 4 subjects with abnormal waveform in the original ballistocardiogram, 3 developed coronary artery disease. Twelve additional subjects who developed coronary artery disease originally had normal waveform but were found to have had a significantly lower estimated cardiac output than did the others in the group. It thus appears that a means is available for detecting coronary artery disease, or perhaps more correctly, myocardial abnormality, earlier than has been heretofore possible.

That absolute cardiac output may be determined by the ballistocardiograph has been frequently questioned. Indeed, Hamilton and co-workers[2, 3] have estimated the pattern of ballistic forces theoretically expected and believe that the maximum instantaneous force should be four times that actually recorded. There is also evidence that the velocity of cardiac ejection is a factor which influences both the form and the amplitude of the ballistocardiogram.[4] Standing waves in the aorta are thought to contribute substantially to the later waves. Despite these apparent handicaps, the ballistocardiograph provides a good empiric measure of cardiac output. Agreement with the direct Fick method[5] is essentially the same as is the agreement of other methods with the direct Fick.[6, 7] The ease of single or serial determinations with this technic contrasts markedly with most other methods.

In any group of normal subjects there are large individual differences in estimated cardiac output even when corrected for surface area as cardiac index (L./min./M.^{2}) or when referred to actual or "ideal" body weight.[1] It would be desirable if means could be found to decrease the dispersion of values in the normal group in order that subjects with abnormally low estimated cardiac index be more readily separated from normal subjects. It was with this thought in mind that the present study was undertaken.

Little attention has been paid to the extrinsic factors which influence the cardiac index as estimated by the ballistocardiograph. Starr and Schroeder[8] require subjects to fast for at least two hours and to rest supine for fifteen minutes before records are taken. These criteria were established after considerable experience in taking ballistocardiograms but no data have been presented confirming them as satisfactory. In fact, by the gas method it has been found that the ingestion of food results in an increased cardiac output lasting as long as six hours, depending upon the amount and nature of the

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food taken. Carbohydrate stimulates the most rapid rise and fall, protein response is slower, and fat is the least effective and slowest stimulant.[9] Smoking is thought to increase cardiac output although the response is small and variable.[11]

According to Tanner the standard error of estimate of stroke volume of one ballistocardiographic determination from another taken five minutes previously is 4.8 per cent.[12] Grollman has reported the cardiac output as determined by the acetylene method to be remarkably constant in duplicate determinations and from day to day in a small number of subjects.[10] He

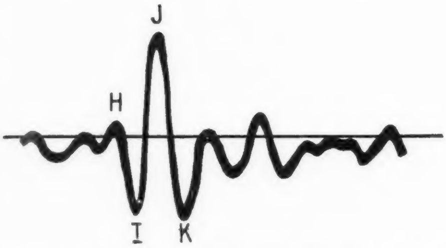

FIG. 1.—A typical ballistocardiographic complex labeled according to the convention.

found this to be true whether studies were performed on a strictly basal or on a fasting "outpatient" basis. Day-to-day reliability of the ballistocardiogram has not been estimated.

METHODS

The ballistocardiograph was of the horizontal high-frequency undamped type.[13] The natural frequency of the bed with respect to its frame was 12.6 cycles per second when loaded with 150 pounds of iron weights. By means of a capacitance pick-up device and a Hathaway S14A oscillograph, records were made on photographic paper. The calibration was such that a force of 280 Gm. applied to the bed caused a displacement of one centimeter on the record. Time lines were recorded at 0.01 second intervals.

There is a considerable respiratory variation in the size of the ballistocardiographic complexes. In reading the records, therefore, (fig. 1) a representative respiratory cycle was determined by inspection and the largest and smallest complexes in that cycle selected for measurement. A baseline was drawn in by inspection from diastolic phase to diastolic phase. The area of the I-wave and of the J-wave in each of the two complexes was approximated by assuming each wave to be a triangle and measuring the altitude from apex to base of each to the closest half-millimeter and the base of each to the nearest hundredth of a second. All measurements were made to the upper border of the tracing in order to avoid errors due to the thickness of the galvanometer spot.

The average areas of the I-wave and J-wave (mm.-sec.) were substituted into Tanner's formula[14]:

Stroke volume in cc./min. $= 100\sqrt{(2\,I \text{ and } J)}\,\sqrt{C}$ *where C represents the duration of a cardiac cycle in seconds.*

$$\frac{\textit{Cardiac output}}{(\textit{L./min.})} = \frac{\textit{Stroke Volume} \times \textit{Pulse Rate}}{1000}$$

$$\frac{\textit{Cardiac index}}{(\textit{L./min./M.}^2)} = \frac{\textit{Cardiac Output (L./min.)}}{\textit{Body surface area } (\textit{M.}^2)}$$

All values were recorded as cardiac index. Body surface area was estimated from height and weight by the DuBois formula.

Means and standard deviations of the distribution were computed for each group of data. Comparisons between determinations made under differing circumstances were made according to the t-test of Fisher.[15] Differences were considered significant at a probability level of 5 per cent or less.

Ten male hospital inpatients were studied who had received intensive (two-day) antiluetic therapy and were afebrile and ambulatory without treatment for at least five days before this study. Ten male laboratory workers were also employed as subjects. All subjects had normal cardiovascular systems by history, physical examination, unipolar electrocardiograms and teleroentgenograms.

The inpatients were kept basal for fifteen hours overnight and in the morning were transferred to the ballistocardiographic bed by surgical cart with as little exertion as possible. They were reassured and kept comfortable but the procedure was unfamiliar to them. After the initial determination, subjects were allowed normal ambulatory activity for the remainder of the day except for a fifteen minute rest prior to each determination. Hourly measurements of cardiac index were made and a substantial standard meal (P, 33 Gm.; CHO, 110 Gm.; fat, 35 Gm.; calories, 888) was eaten from 11:30 to 11:45 A.M. No other food intake was allowed throughout the day and smoking was forbidden. Water was allowed ad lib. Beginning at 2:45 P.M., determinations were made at five-minute intervals while resting supine for forty minutes. The entire routine was repeated the following day.

The "outpatient" laboratory personnel were similarly studied but they were allowed to spend the night at home and came to the laboratory in the fasting state. All were familiar with the procedure and they were studied one day only.

The mean age of all subjects was 24.4 years; mean surface area was 1.84 M.²

Results

The mean basal cardiac index of 20 subjects was 3.35 L./min./M.^{2} (standard deviation of the distribution = 0.54 L./min./M.^{2}), which compares favorably with values published for the method of right heart catheterization by Cournand and co-workers[16] of 3.12 and by Stead and co-workers[17] of 3.30 L./min./M.^{2}.

After the subjects were allowed to be ambulatory, but while they were still fasting, there was no change in the cardiac index (fig. 2, compare values at 9:00 and 10:00 A.M.).

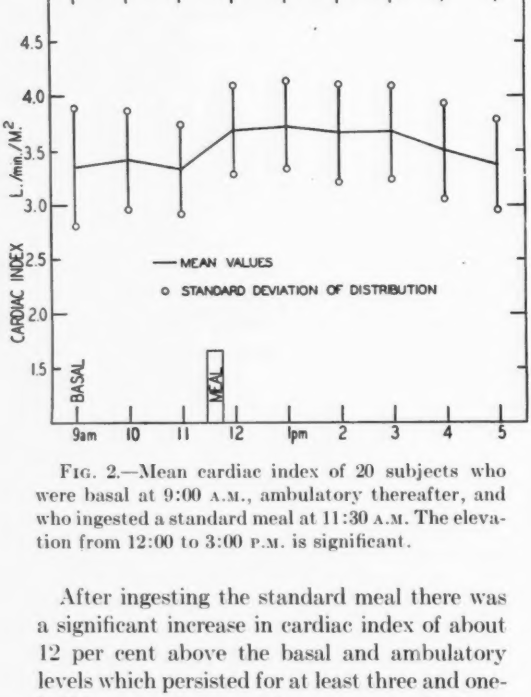

Fig. 2.—Mean cardiac index of 20 subjects who were basal at 9:00 A.M., ambulatory thereafter, and who ingested a standard meal at 11:30 A.M. The elevation from 12:00 to 3:00 P.M. is significant.

After ingesting the standard meal there was a significant increase in cardiac index of about 12 per cent above the basal and ambulatory levels which persisted for at least three and one-half hours and appeared to return to the baseline only after five and one-half hours (figs. 2 and 3).

In view of the demonstration by Hickam and co-workers[18] that the tension of impending academic examinations increased cardiac index in their subjects, emotion might be expected to be a factor in routine ballistocardiography. In this case, however, all mean values throughout the second consecutive day were not significantly changed from those of the first day (fig. 3).* Furthermore, the mean pulse rate was 64 per minute and the highest noted on any occasion was 84 per minute. Nor did subjects familiar with the procedure, the "outpatients," differ from those unfamiliar with it, the hospital inpatients (fig. 3). The laboratory personnel also spent the night at home prior to study and still did not differ from the strictly basal subjects.

Determinations made within one minute of reclining and at short intervals thereafter for forty minutes showed no significant change (fig. 4). It thus appears that the ballistocardiogram can be recorded as soon as the subject is comfortable and the apparatus adjusted.

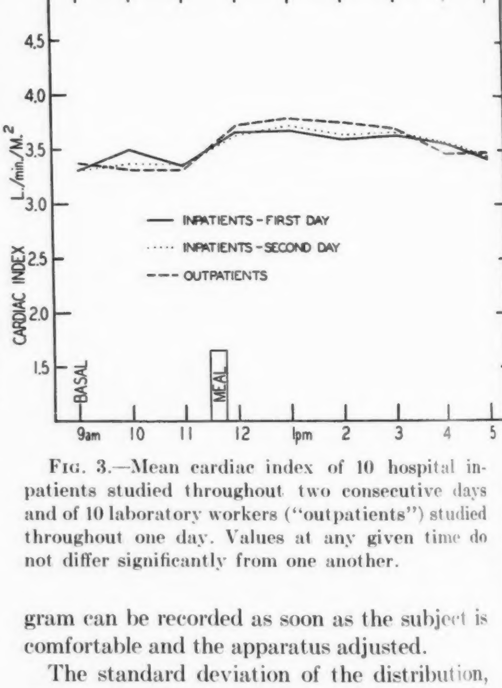

Fig. 3.—Mean cardiac index of 10 hospital inpatients studied throughout two consecutive days and of 10 laboratory workers ("outpatients") studied throughout one day. Values at any given time do not differ significantly from one another.

The standard deviation of the distribution, representing the dispersion of values about the mean, was not significantly diminished under any of the circumstances of study.

Duplicate selections of complexes and dupli-

*On scattered occasions in this laboratory, as much as a 50 per cent increase in cardiac index has been observed in response to emotional stimuli other than those attendant to taking ballistocardiograms. The possibility of such influence in some subjects must be kept in mind but is probably not important in routine ballistocardiography.

cate calculations by the same or by a second observer demonstrated no systematic error to

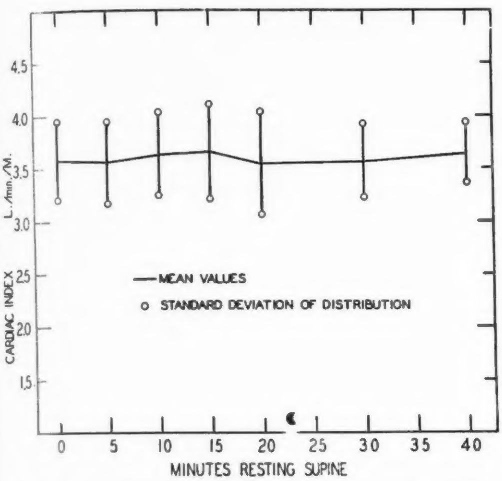

FIG. 4.—Mean cardiac index of 10 subjects resting supine. Determinations made within one minute after reclining did not differ significantly from those made in the following forty minutes.

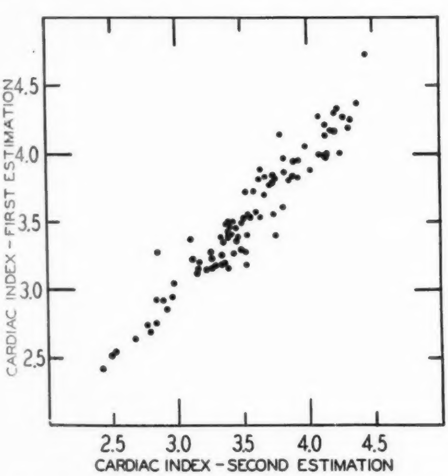

FIG. 5.—Scatter plot of duplicate determinations by the same observer from different respiratory cycles of the same record. Mean of first estimations = 3.56. Mean of second estimations = 3.54. N = 90. Correlation coefficient = .93. Standard error of estimate = 0.168 L./min./M.².

be introduced by the observer (figs. 5 and 6). Doubling the number of measured complexes decreased the standard deviation of the distribution only from 0.468 L./min./M.² to 0.457 L./min./M.² (N = 162).

A statistical analysis of variance[19] was performed on the data obtained from 7 subjects while resting supine for 20 minutes.* The results are shown in table 1. In order of decreasing importance, the following factors were found to contribute to the total variance: (1) the subjects, (2) interaction between subject and time, and the factor time itself, and (3) residual error. The same relationship is found when the

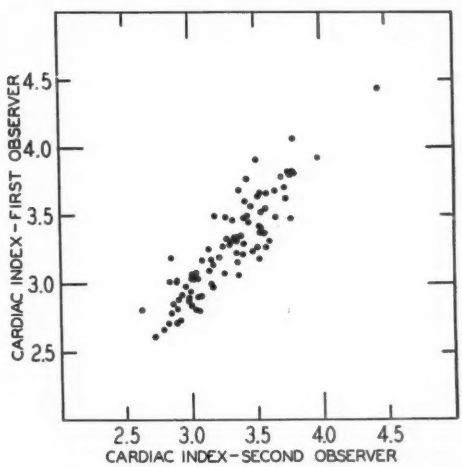

FIG 6.—Scatter plot of duplicate determinations by different observers from different respiratory cycles of the same record. Mean of first observer = 3.65. Mean of second observer = 3.68. N = 90. Correlation coefficient = .91. Standard error of estimate = 0.191 L./min./M.².

effect of eating is also included. This demonstration that the differences between individuals are greater than other sources of variance even in normal subjects lends encouragement to future attempts to distinguish between individuals by means of the ballistocardiogram.

*The analysis of variance is a statistical device for determining the significance of the contribution of different sources to the total variation in a set of observations. In this case, duplicate determinations on each of 7 subjects were performed at five-minute intervals for twenty minutes. The data were arranged in a grid configuration and the proportion of the total variance due to each factor (individual differences in subjects, time of measurement in the series, interaction between subjects and time, and residual error) was computed.

The residual error includes that of measurement of complexes and particularly when one is presented with a small number of ballistocardiographic complexes per respiratory cycle from which to choose. Obviously it is the unusual cycle in which complexes occur by chance at exact maximum and minimum amplitude.

A quantitative estimate of the day-to-day variability is not possible with the data at hand. It appears, however, to be little greater than that between two determinations made at five-minute intervals.

TABLE 1.—*Analysis of Variance.*[19] *Seven subjects. Duplicate determinations were made at five-minute intervals for twenty minutes.*

	Sum of Squares	Degrees of Freedom	Variance
Subjects	13.403	6	2.234
Interaction between subjects and time	1.880	24	.078
Time	.185	4	.046
Residual error	.406	35	.012
		69	
	F	**Probability**	
Subjects/Interaction	28.	< .01	
Interaction/Time	1.7	> .05	
Time/Residual error	4.0	< .01	

CONCLUSIONS

In order to attain the least variation consistent with economy of effort, the ballistocardiogram should be recorded as follows:

1. Subjects may be allowed to stay at home overnight, and may be ambulatory, but they should fast at least three and one-half and probably five and one-half hours before the records are made.

2. Records may be taken as soon as the subject is comfortable and the apparatus is adjusted.

3. Unfamiliarity with the procedure on the part of the subjects does not appear to be important. Under ordinary circumstances the effect of emotion is negligible.

4. Only one set of calculations by one observer is necessary per determination.

ACKNOWLEDGMENTS

The technical assistance of Catharine Benjamin and Jesse Yaffa is gratefully acknowledged. Dr. James E. Birren made valuable statistical suggestions and general criticisms of this paper.

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Diagnosis of Coarctation of the Aorta with the Aid of the Low Frequency, Critically Damped Ballistocardiograph

By J. L. Nickerson, Ph.D., G. H. Humphreys, M.D., R. A. Deterling, M.D., T. C. Fleming, M.D., and J. A. L. Mathers, M.D.

Ballistocardiograms taken with the low frequency, critically damped ballistocardiograph on 17 patients having coarctation of the aorta have a characteristic pattern in which the K wave is absent. In the patients in whom the coarctation was surgically removed, the pattern returned toward the normal type with reappearance of the K wave.

A RECENT study by Nickerson[1] of the origin of the K wave of the ballistocardiogram has indicated that interference with the flow of blood down the descending aorta diminishes or eliminates this wave. The purpose of the present article is to report the ballistocardiographic findings in a series of patients with coarctation of the aorta and to demonstrate the changes in pattern appearing after surgical repair of the defect.

The probability of the existence of a coarctation in all these patients was decided by clinical examination, and a ballistocardiogram under basal conditions was made. The ballistocardiograph used was the low-frequency, critically damped instrument designed by Nickerson and Curtis[2] and tested by comparison with the direct Fick method by Nickerson, Warren, and Brannon.[3] Ballistocardiograms were also made postoperatively on those patients on whom operative procedures were undertaken. The first of these records was usually made about two weeks after operation and subsequent records were made when the patient returned to the hospital for examination. The records were made both with and without breath-holding, the cardiac output being computed from the records made during quiet breathing. Electrocardiograms were recorded simultaneously with the ballistocardiograms.

Seventeen patients with clinical diagnosis of coarctation of the aorta were studied. These patients ranged from 4 to 48 years of age with 13 of them in the second and third decade of life. Three of these patients were without symptoms while 14 had symptoms varying from slight fatigue on walking to pain, palpitation, coldness of the lower extremities, weakness, and dizziness. Two patients showed mental retardation.

Before operation the resting blood pressure in the upper extremities was in general high, ranging from 139/90 to 230/110, with an average for the whole group of 169/93. The pressure in the lower extremities was obtainable in only 6 of the patients and in these the systolic value averaged 72 mm. below the values in the upper extremities.

After operation the patients so treated showed an average fall from their preoperative pressures of 21 mm. systolic and 6 mm. diastolic in the upper extremities. The pressures in the lower extremities in these patients had become measurable after operation with a systolic value averaging 16 mm. below the upper-limb postoperative systolic pressure, and a diastolic pressure averaging 9 mm. above the upper-limb postoperative diastolic pressure.

Seven patients showed no notching of the ribs. Four patients showed minimal notching while the remaining 6 had marked notching

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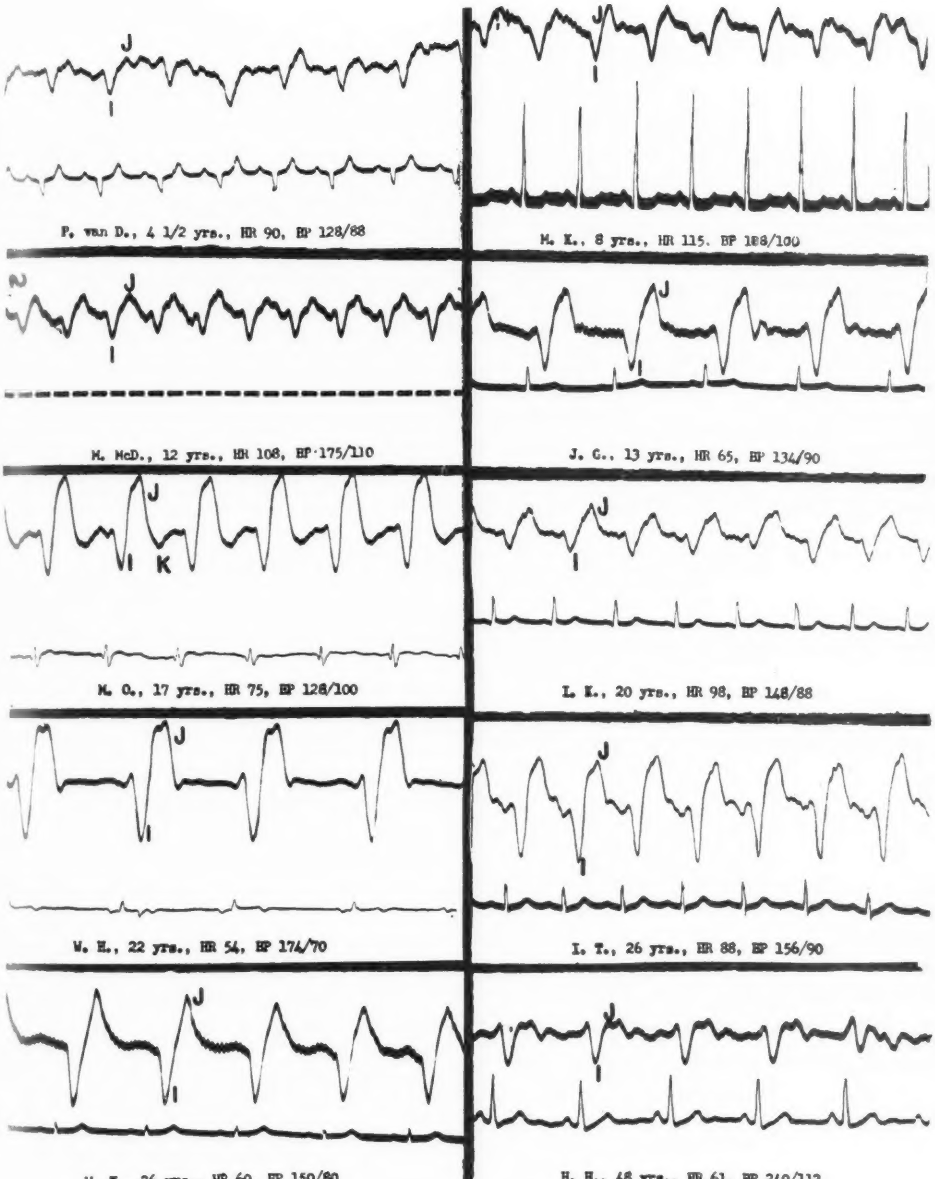

FIG. 1.—Ballistocardiograms made with the low-frequency, critically damped ballistocardiograph on a group of patients with clinically diagnosed coarctation of the aorta.

of the ribs. The angiocardiogram demonstrated coarctation definitely in 10 patients while 3 had questionable narrowing of the large vessel. In one patient only, the presence of large collateral vessels was shown without corresponding narrowing of the aorta. In one patient the

angiocardiogram showed no abnormality although a coarctation was demonstrated at operation. In 2 patients angiocardiograms were not made.

In addition to the finding of coarctation of the aorta at operation, 3 patients showed aortic insufficiency and two patients, patent ductus arteriosus.

The ballistocardiographic patterns of all these subjects with coarctation show one striking feature in common, namely, the absence of the K wave. The ballistocardiograms of the patients upon whom operation was not performed are shown in figure 1. The pre- and postoperative ballistocardiograms of the patients having surgical repair of the coarctation are shown in figure 2. The generation of the K wave appears to be due mainly to the footward impact, produced when the systolic rush of blood down the descending aorta is slowed in its course by its accumulation in the lower portions of this vessel. When the aorta is constricted, this rush of blood is absent and absent also is the impact which would carry the critically damped system across the base line of the pattern to produce the K wave.

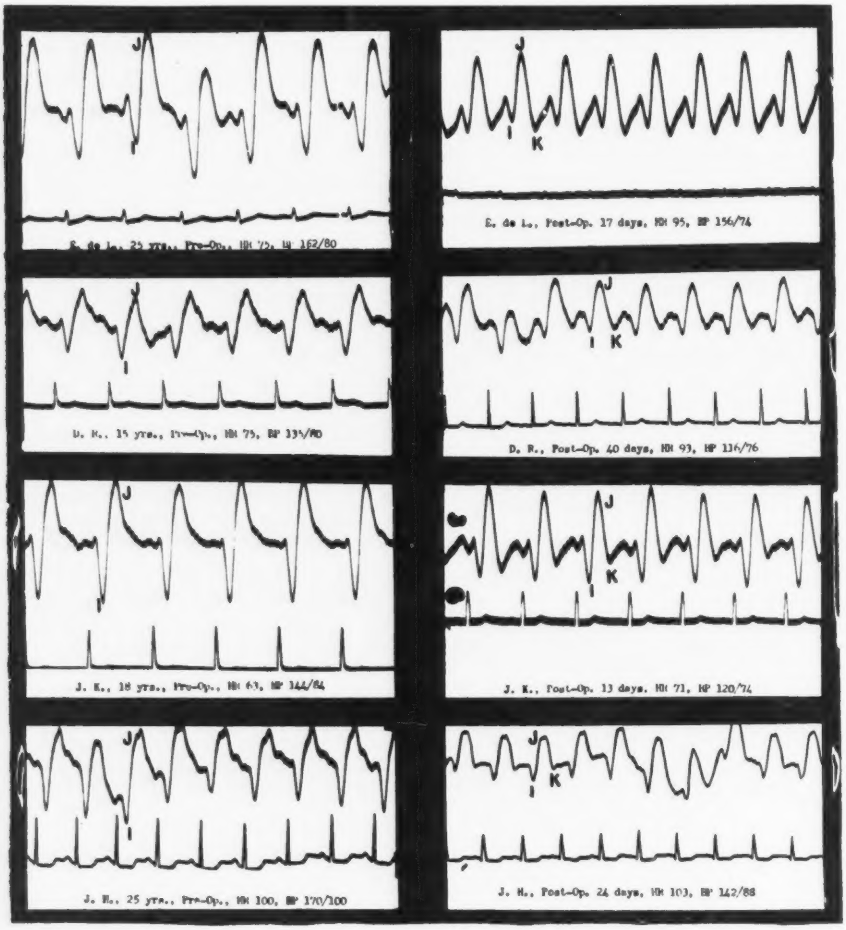

FIG. 2.—Ballistocardiograms made before and after operation on patients with coarctation of the aorta.

An examination of figure 2 shows that the operative procedures which improve the flow of blood down the descending aorta also restore the ballistic pattern toward normal with the appearance of a K wave. Patient J. H., in whom the early postoperative pattern showed only a small K wave, has now, a year later, a well-developed K wave (fig. 3). This patient had a subclavico-aortic anastomosis and the improvement is probably due to the gradually increasing effectiveness of the new aortic channel.

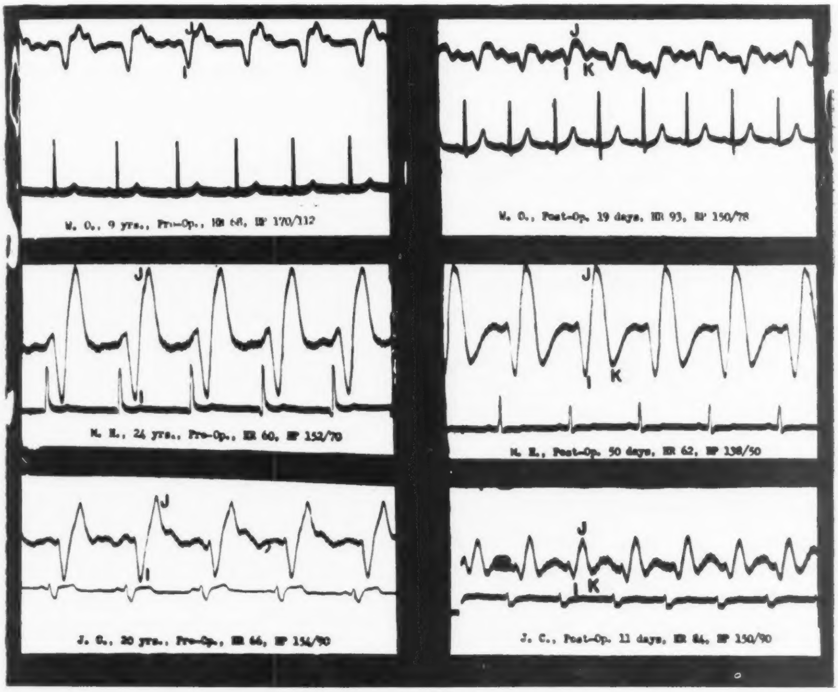

FIG. 2.—Cont'd.

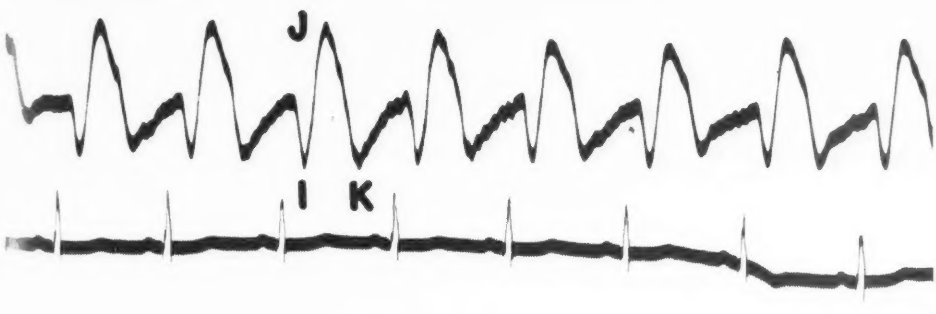

FIG. 3.—Ballistocardiograms on Patient J. H. of figure 2 made one year after operation.

Similar observations on the absence of the

K wave in coarctation of the aorta were reported recently by Brown, Hoffman, and De Lolla[4] using a ballistocardiograph of the Starr type (high-frequency and undamped). However, in our experience the coarctation type pattern is more clearly and consistently shown in the critically damped system than with the undamped system.[1]

Summary

The recording of low-frequency, critically damped ballistocardiograms of 17 patients with clinically diagnosed coarctation of the aorta shows in all the patients a pattern characteristic of the syndrome. This characteristic sign is the absence of the K wave of the pattern. In the 7 of these patients on whom operative removal of the coarctation was performed, the pattern shows a return to normal with restoration of the K wave.

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Electrokymographic Studies in Insufficiency of the Aortic and Pulmonic Valves

By Howard E. Heyer, M.D., Ernest Poulos, M.D., and Julian H. Acker, M.D.

The following paper describes the results of electrokymographic studies performed on patients with proved aortic insufficiency. Alterations in the shape of the aortic ejection curve were found and were accompanied by a diminution or absence of the incisura in the presence of insufficiency of the aortic valves. Alterations in heart border motion of the ventricles were also found. The possible dynamic factors responsible for these changes are discussed and the clinical application of the electrokymograph to aortic and pulmonic valvular disease is pointed out.

SINCE Corrigan's[1] description of the water-hammer pulse of aortic insufficiency in 1832, numerous studies of the alterations in circulatory dynamics have been reported. In human beings, MacKenzie[2] recorded, by means of the polygraph, the characteristics of the peculiar pulse present in association with this disease. Feil,[3] using optical methods of recording, has obtained recordings of the arterial pulse wave in patients similar to those recorded by MacKenzie. By means of the roentgenkymograph, records of the border motion of the heart and great vessels have been obtained in patients with aortic valvular disease.[5] The roentgenkymographic method has certain inherent limitations, however, including the relative crudeness of the method of recording, and the difficulty of obtaining accurate measurements of the duration of various portions of the cardiac cycle for any given chamber or vessel. Although careful studies, utilizing optical means of recording, have been made of the pressure pulses in the ventricle and aorta of animals with artificially induced aortic insufficiency, such direct methods of recording have not been systematically recorded in the human patient.

Recently Henny, Boone, and Chamberlain[6] have introduced an accurate method of recording the border motion of the heart and great vessels by means of the electrokymograph. Tracings of the ventricular border motion recorded optically with this instrument have revealed a marked similarity to volume curves of the heart obtained in animals by means of the cardiometer. Records of border motion of the great vessels closely resemble those obtained from intra-aortic pressure tracings.

It is the purpose of the present study to record the alterations from the normal in such tracings, obtained by means of the electrokymograph, in a group of patients suffering from insufficiency of the aortic and pulmonic valves. Evidence will be presented that tracings of the great vessels with insufficient valves reveal a characteristic contour, and that the records of ventricular border movements in some patients may also show certain alterations. In addition, data indicative of alterations in the duration of certain portions of the cardiac cycle will be presented. Finally, the ability to determine the site or origin of a parasternal diastolic murmur (i.e., to ascertain whether insufficiency of the aortic or pulmonic valve exists) by means of such electrokymographic tracings will be illustrated.

Method and Material

The apparatus used consisted of the 931-A GE photo-electron multiplier tube and potentiometer (as described by Henny and co-workers[6]), Cambridge electrocardiograph (with sound and pulse recorder), and a fluoroscope with a tilting table. Eighty kilovolts and 4 milliamperes were used, and the electrocardiograph paper was run at 50 mm. per second. The galvanometer string was standardized so that 1 millivolt gave a 2-cm. deflection. The coarse adjustment of the potentiometer was set at 5 while the setting of the fine adjustment was varied for the individual. The tracings were recorded in the posteroanterior, left anterior oblique, and right

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anterior oblique views. The 30 normal subjects were medical students ranging from 19 to 30 years of age. Twenty-two patients with aortic insufficiency from the outpatient and ward services of Parkland Hospital were studied. The patients ranged from 14 to 65 years of age. Of those with valvular disease, in 6 the origin was rheumatic and in 16 syphilitic. In each patient with aortic disease, definite clinical evidence of insufficiency was present, with characteristic blowing diastolic murmurs, frequently associated with evidence of alterations in the peripheral pulses, frequently with large pulse pressures, and with signs of left ventricular enlargement in all patients. Tracings of the aortic knob, ascending aorta, pulmonary artery, pulmonary artery segment, right and left auricles, and right and left ventricles were made.

Results of Electrokymographic Tracings

Aortic Insufficiency

Ascending Aorta. The tracings of the ascending aorta were satisfactorily obtained in 15 patients and are described in the following paragraphs according to contour and to duration of the ejection phase.

The majority of the tracings showed a moderately rapid, smooth, and continuous upswing of the first major upward deflection, followed by a rounded or somewhat flat peak, and terminating in a downward direction with the beginning of the phase of reduced ejection (fig. 1, *C*). The appearance of the early stages of ejection was, in many cases, not materially different from that of the normal tracing. However, in four of the tracings the initial rising limb was extremely thin and rose rapidly to a high summit (fig. 1, *B*).

The most constant and striking finding noted in these tracings was that there was marked diminution (fig. 1, *B*) to complete absence (fig. 1, *C*) of the incisural notches in all instances. In most cases this vestigial incisura occurred farther down on the descending limb than normally, as has been reported by other methods of investigation in animals.[9, 10] In those cases in which the incisura was markedly diminished to absent, the descending limb of the aortic tracing revealed a rapid, smooth descent to the base line, beginning with the phase of protodiastole (fig. 1, *C*). When the rate of decline in aortic volume in diastole was observed in various cases, it appeared that the maximal decline occurred earlier in diastole in the phases of protodiastole and isometric relaxation in the patients with valvular insufficiency of the great vessels than in the normal subjects. In the normal group, aortic volume often appeared to decline to a greater degree in later diastole than in those patients with aortic or pulmonic insufficiency.

The phases studied were total, rapid and reduced ejection. Since the incisuras of the aortic tracings were diminished or absent, this landmark for determining the end of systole was often not available. Total ejection in the ascending aorta, therefore, was determined by measuring the time consumed from the beginning of the rising limb of the tracing to the first vibration of the second sound.* Rapid ejection was measured as the period from the beginning of the rising limb to the summit of the tracing. Reduced ejection was measured from the summit to the second sound. It will be seen from figure 2 that the duration of the period of total ejection was prolonged in a majority of the patients with aortic insufficiency, when compared with the normal subjects. Rapid and reduced ejection were not selectively increased, either or both being prolonged in various instances.

The above findings were true in patients who had aortic insufficiency caused by either rheumatic fever or syphilis. There was no apparent close correlation with duration of the disease process, age of the patient, pulse pres-

* We have found the beginning of the second sound usually to be coincident with the beginning of closure of the aortic valves, with the beginning of the phase of protodiastole (the earliest phase of diastole), and thus with the end of ejection in the ascending aorta. Owing to ventricular asynchronism, in some patients the right ventricle may cease contraction first, and thus closure of the pulmonic valves would give rise to the earliest components of the second sound. In such cases the end of systole in the left ventricle would actually occur slightly later than the onset of the second sound would indicate. In such instances, however, measurements from the beginning of the ejection limb to onset of the second sound would give a value which might be slightly less than the true duration of total ejection, but would not give values that were greater than the actual duration. Hence total ejection may be measured with a fairly high degree of accuracy by this method.

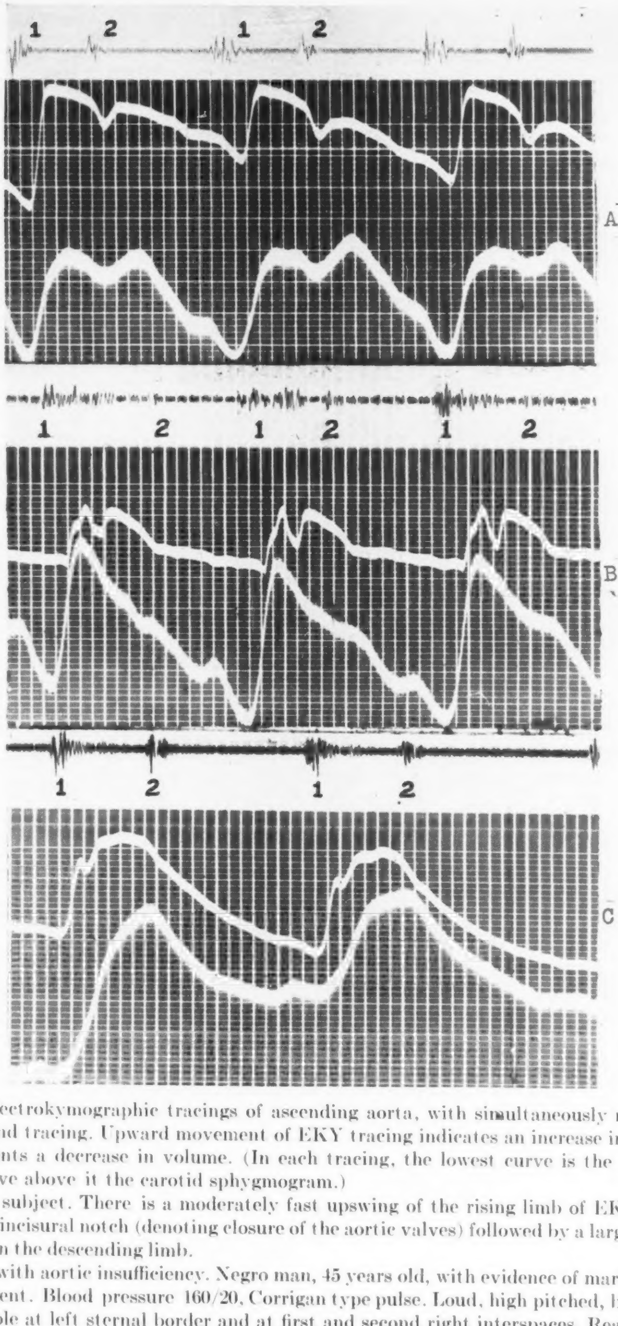

FIG. 1.—Electrokymographic tracings of ascending aorta, with simultaneously recorded carotid pulse and sound tracing. Upward movement of EKY tracing indicates an increase in volume, downward movements a decrease in volume. (In each tracing, the lowest curve is the ascending aorta EKY, the curve above it the carotid sphygmogram.)

A, Normal subject. There is a moderately fast upswing of the rising limb of EKY tracing, with a well marked incisural notch (denoting closure of the aortic valves) followed by a large rebound wave, located high on the descending limb.

B, Patient with aortic insufficiency. Negro man, 45 years old, with evidence of marked left ventricular enlargement. Blood pressure 160/20, Corrigan type pulse. Loud, high pitched, blowing diastolic murmur audible at left sternal border and at first and second right interspaces. Reactions to Kline, Wassermann and Mazzini tests positive for syphilis. Note sharp, rapid increase in volume in early ejection phase, followed by a rapid decline in volume. There is a vestigial incisura located far down on the descending limb of the tracing. The incisural notch of the carotid pulse, although diminished in depth, is more easily distinguished than the incisura of the aorta in most pulse waves.

C, Patient with aortic insufficiency. Negro woman, 51 years old, with moderate left ventricular enlargement; vigorous, hyperactive carotid pulsations; moderately loud, high-pitched blowing diastolic murmur at left sternal border and at first and second right interspaces; rather harsh systolic murmur at first and second right interspaces. Reactions to Kline and Wassermann tests positive. There is a rather gradual rise of the pulse wave, with a fairly rapid decline after the summit. There is no clearly distinguishable incisural notch, on either aortic EKY or carotid pulse, to denote closure of aortic valves. (In tracings 1, *B* and 1, *C*, as in subsequent tracings, the diaphragm of the sound recorder has been placed laterally, over the apex of the heart, rendering the diastolic aortic murmur almost indistinguishable.)

sure, presence or absence of signs of congestive failure, or with the ingestion of digitalis.

Aortic Knob. The tracing of the aortic knob was satisfactorily obtained in 20 patients and these manifested definite changes from the normal. As was the case in the ascending aorta, the incisural notches were remarkably diminished (fig. 3, *B*) or entirely absent (fig. 3, *C*). The rising limb was not steep, as has been described above in several cases, but was as gradual as the normal. The peak was rounded but rarely flat as in some of the ascending aorta tracings.

Ventricle. There were 16 left ventricular tracings which were susceptible to analysis. The general contour of the systolic portion of the tracing was not altered. However, the diastolic section of the curves frequently showed aberrations from the normal. The periods of isometric relaxation, rapid filling, and diastasis usually show well-defined changes in gradient in the electrokymographic tracings of the ventricles of normal subjects (fig. 4, *A*). In place of the normal contour of the ventricular curve, there was frequently a rather smooth continuous upswing with poor delineation of the phases of rapid filling, diastasis, and auricular systole (fig. 4, *B* and *C*). The phase of diastasis was sometimes present provided the rate was sufficiently slow. It should be noted that while the curves of the ascending aorta were diagnostic, those of the left ventricle were less so. Although these left ventricular tracings were often altered as described above, in some patients their contour appeared normal.

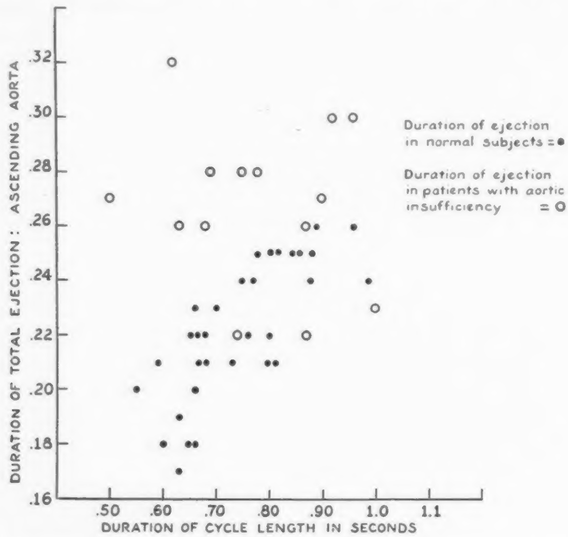

FIG. 2.—Electrokymographic tracings of ascending aorta. Duration of ejection phase in patients with aortic insufficiency (open circles) compared with that of normal subjects (solid black circles). The duration of ejection is longer in most patients with aortic insufficiency than in normal subjects with comparable cycle lengths.

Carotid Artery. The tracings of the carotid artery, obtained by placing a cup against the vessel and utilizing a segment capsule with optical recording, usually showed a contour similar to that of the aortic electrokymogram, with a diminished or absent incisura which frequently occurred low on the descending limb of the pulse wave. However, a point of some interest was the finding that in a few patients with aortic insufficiency incisural notches were sometimes present on carotid tracings even though they were completely absent on the electrokymographic tracings of the aortic knob (fig. 6, *B*). Although no explanation was apparent to account for this persistence of the carotid incisural notch under such conditions,

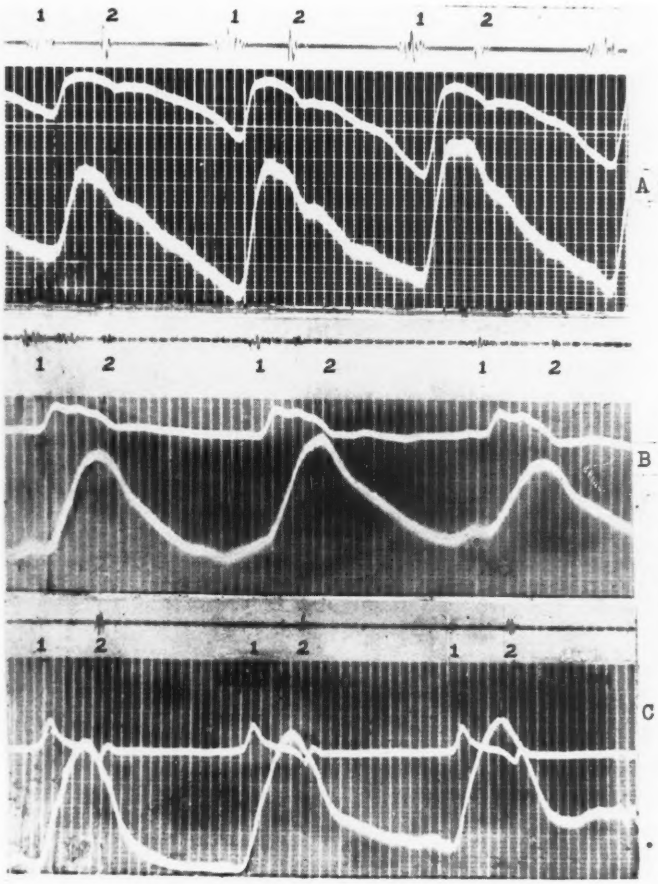

FIG. 3.—Electrokymographic tracings of aortic knob. (In each tracing, the lowest curve is the aortic knob EKY, the curve above it the carotid sphygmogram.)

A, Normal subject with well marked incisura denoting aortic valve closure.

B, Patient with aortic insufficiency; 58 year old woman. Blood pressure 140/62; marked left ventricular enlargement with loud blowing diastolic murmur audible at first and second right interspaces and at left sternal border. Numerous previous arm and hip injections for syphilis; reactions to serologic tests at time of examination negative. There is a poorly marked vestigial incisura seen on aortic knob EKY. The incisural notch is slightly better marked in the carotid pulse.

C, Patient with aortic insufficiency; Negro man, age 47 years. Admitted with acute polyarthritis diagnosed as acute rheumatic fever; history of "leakage of heart" known for twenty years. Blood pressure 180/80; diastolic blowing murmur at first and second right interspaces. Reaction to Mazzini test negative. Descending limb of EKY shows marked and abrupt decline in aortic volume with practically absent incisural notch. The greatest decline in aortic volume is seen to occur in early diastole. There is a well marked carotid incisura.

it would suggest that the aortic electrokymogram was a more reliable method of determining alterations in the pulse wave contour than was the carotid artery tracing obtained by these means. The periods of rapid ejection were variable on the carotid artery records, and their contour often differed considerably from that of the aortic tracings.

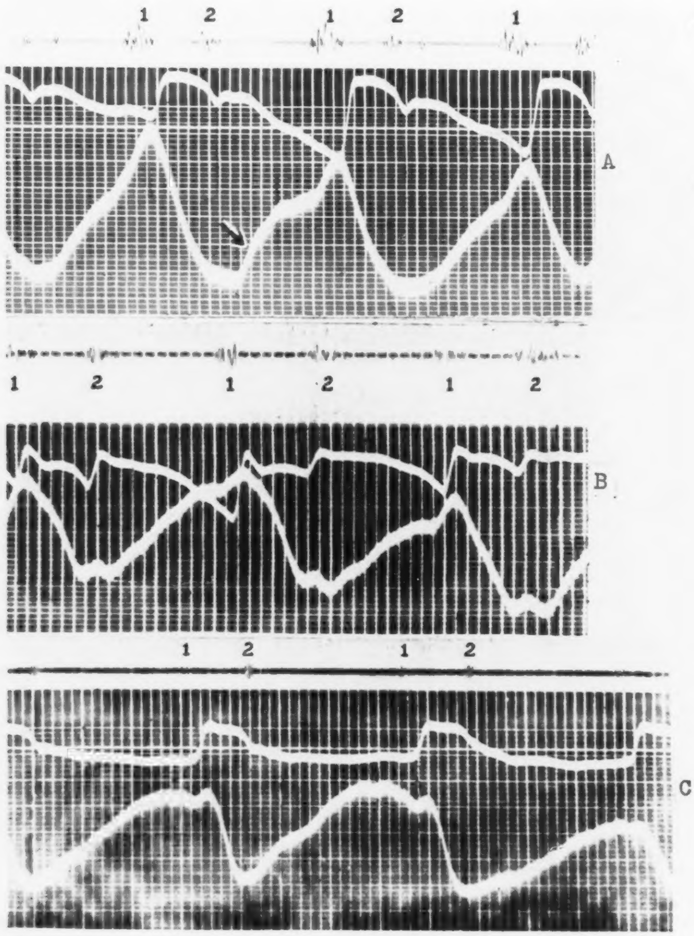

FIG. 4.—Electrokymographic tracings of left ventricle. Downward limb of EKY indicates a decrease in volume accompanying systole, upward movement indicates an increase in volume in diastole. (In each tracing, the lowest curve is the left ventricle EKY, the curve above it the carotid sphygmogram.)

A, Normal subject. Arrow denotes sharp and well defined increase in volume in rapid-filling phase of diastole, due to normal filling from auricle, followed by resting phase of diastasis and by terminal increase in ventricular volume probably due to auricular systole.

B, Patient with aortic insufficiency and previous congestive failure; Negro man, age 59 years. Moderate left ventricular enlargement, diastolic murmur audible at left sternal border and second right interspace. Blood pressure 120/56. Reactions to Kline, Wassermann and Mazzini tests positive. Phases of rapid filling and diastasis are poorly delineated with a somewhat smooth, continuous upswing in diastole. Note well defined incisural notch of carotid pulse.

C, Patient with aortic insufficiency; Negro man, age 40 years. Marked left ventricular enlargement, hyperactive carotid pulsations, blood pressure 150/76. Loud, blowing diastolic murmur at left sternal border and upper right sternal margin. Wassermann reaction 4+. As in the previous patient, the rapid filling phase and phases of diastasis and auricular filling are poorly marked and replaced by a rather gentle upward gradient of filling of the ventricle.

Additional Findings.

Pulmonary Insufficiency. In one patient whose clinical diagnosis was tetralogy of Fallot, angiocardiographic studies demonstrated a stenosis of the pulmonary artery. The patient also had a loud, well defined diastolic, blowing murmur heard at the base of the heart and along the left sternal border, with normal pulse pressure, and with no peripheral signs of aortic insufficiency. Electrokymographic tracings of the pulmonary artery in this patient showed the absence of an incisural notch (fig. 5, *B*)

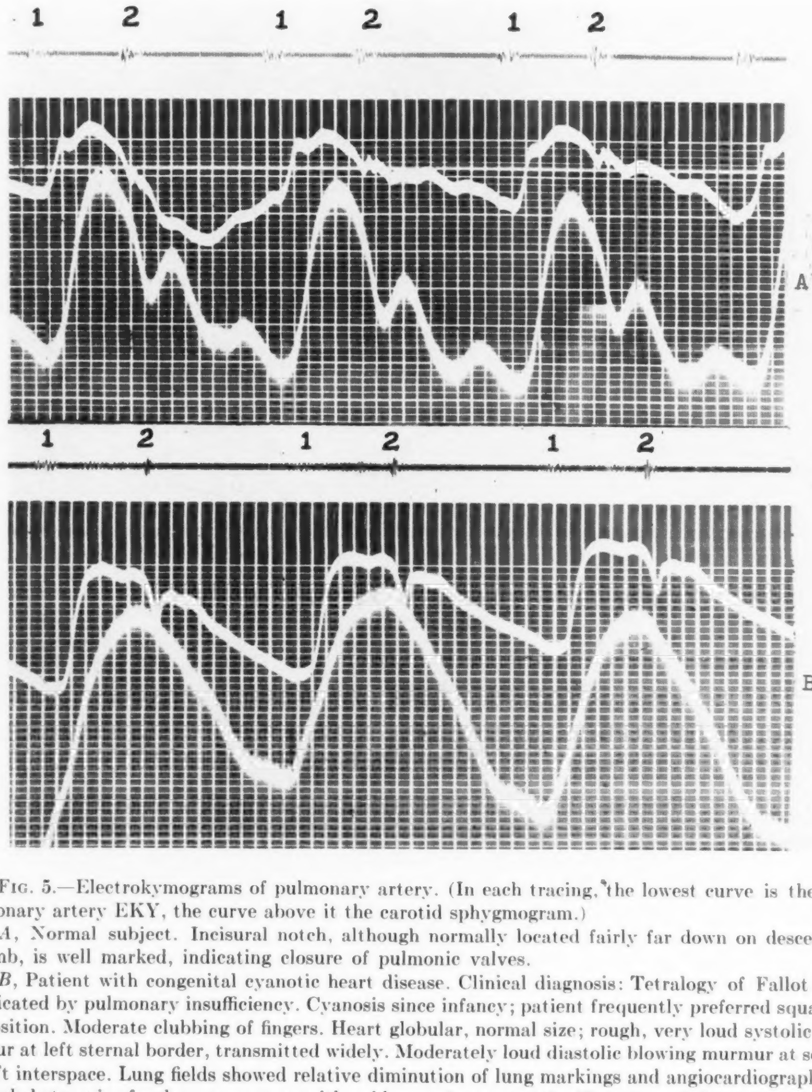

FIG. 5.—Electrokymograms of pulmonary artery. (In each tracing, the lowest curve is the pulmonary artery EKY, the curve above it the carotid sphygmogram.)

A, Normal subject. Incisural notch, although normally located fairly far down on descending limb, is well marked, indicating closure of pulmonic valves.

B, Patient with congenital cyanotic heart disease. Clinical diagnosis: Tetralogy of Fallot complicated by pulmonary insufficiency. Cyanosis since infancy; patient frequently preferred squatting position. Moderate clubbing of fingers. Heart globular, normal size; rough, very loud systolic murmur at left sternal border, transmitted widely. Moderately loud diastolic blowing murmur at second left interspace. Lung fields showed relative diminution of lung markings and angiocardiography revealed stenosis of pulmonary artery with evidence of poststenotic dilatation. (Subsequent Blalock-Taussig procedure performed, with marked improvement in cyanosis and well-being.) Note complete absence of incisura on descending limb, with sharp and well defined incisura of carotid pulse. The electrokymographic tracings of the aorta in this patient (not shown) revealed a well defined incisural notch.

while the tracings obtained from the aorta definitely exhibited these notches. Normal pulmonary artery tracings, as seen in figure 5, *A*,

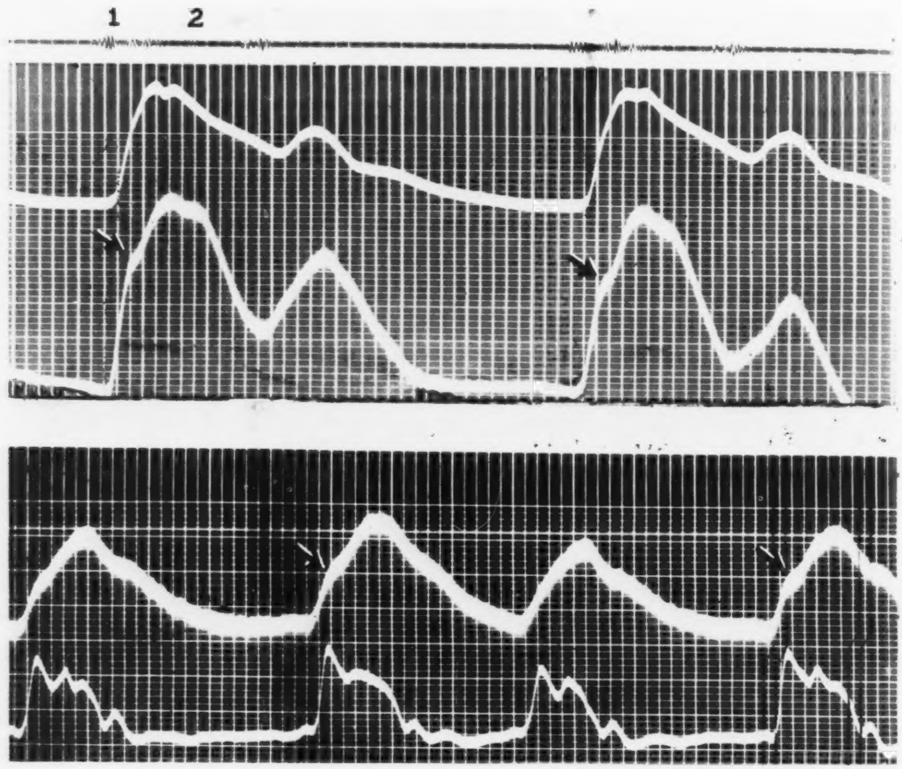

Fig. 6.—Patients with aortic stenosis and aortic insufficiency. (In each tracing, the lowest curve is the ascending aorta EKY, the curve above it the carotid sphygmogram.)

A, EKY of ascending aorta in 31 year old man with aortic stenosis. History of "inflammatory rheumatism" at age 9 years. Marked cardiac enlargement; very loud harsh systolic murmur at first right interspace transmitted into neck vessels, followed by blowing diastolic murmur in same area. After an initial ejection phase of rapid increase in volume there is a well defined change in gradient (indicated by arrows) with more gradual increase in volume to the summit. The descending limb shows no definite incisural marking. Immediately following the larger pulse waves are smaller ones due to premature ventricular contractions.

B, Patient with aortic stenosis and insufficiency; 64 year old white woman. Acute rheumatic fever in early adult life, recent congestive failure. Marked cardiac enlargement. Harsh systolic murmur at first right interspace, transmitted into neck vessels; blowing diastolic murmur in same area, also audible at left sternal margin. Separate harsh systolic and rumbling diastolic murmurs at apex. Reactions to serologic tests for syphilis negative. Note similar change in gradient of ascending ejection limb and poorly defined incisural notch of descending limb. In figure 6, *B* the incisural notch of carotid pulse is well defined.

show a definite incisural notch. There appeared to be no doubt, therefore, that the murmur noted was due to insufficiency of the pulmonic rather than the aortic valves.

Aortic Stenosis. In 2 patients there was definite clinical evidence of aortic stenosis complicating the aortic insufficiency. In these two patients the rapid ejection period of the ascending aorta was divided into two separate phases—an initial rapid upswing ending abruptly in a much slower rise upward (fig. 6, *A* and *B*).

Tracings of the central arterial pulse, recorded optically in patients with aortic stenosis, have shown a strikingly similar contour.[3–4]

Discussion

The electrokymograph has provided an easy and accurate method of studying many aspects of circulatory dynamics in patients. Many of these data are otherwise only obtainable by complicated procedures which are undesirable or involve some discomfort or hazard. Thus, although the registration of pressure pulse curves from the aorta, via catheterization of a peripheral artery, has been found possible in human beings, it is a relatively dangerous procedure.[22]

It should be realized that the electrokymogram provides information regarding the heart and great vessels through changes in volume, caused primarily by the movement of blood through the chambers of the heart and the great vessels. The electrokymogram has been shown to yield tracings closely resembling intra-aortic and intrapulmonic pressure curves obtained by the direct insertion of cannulas into the great vessels in animals or by cardiac catheterization in human beings.[7, 8] Electrokymographic tracings recorded from the ventricles have been shown to resemble closely ventricular volume curves provided by the cardiometer.[7, 8] Although positional movements of the heart and great vessels interpose some artefacts in the tracings from both instruments, nevertheless the general resemblance to records obtained by more direct means is striking, and the time relationships of the major events of the cardiac cycle are faithfully preserved.

The most striking alteration in aortic tracings obtained from patients with aortic insufficiency was the abolition or marked diminution in the incisural marking which normally accompanies the closure of intact aortic valves. Although a close correlation between the estimated degree of valvular insufficiency and the extent of obliteration of incisural marking was not possible, in general the more severe the evidence of valvular incompetency, the more completely this normal landmark was obliterated. This was accompanied by a rapid decline in aortic volume in the early phases of diastole. The classic studies of Wiggers and his associates[9–14] in animals, utilizing aortic pressure curves, have shown similar findings in experimental aortic insufficiency in animals. Their experiments have shown that the early diastolic decline in pressure increases significantly in experimental aortic insufficiency, and that the abruptness of the pressure decline increases with the size of the leak. Furthermore, these authors have shown that with larger leaks a progressively greater percentage of the regurgitated blood re-enters the ventricle earlier in diastole, in the protodiastolic phase. In this connection it should be pointed out that the percentage of blood that regurgitates per beat varies with the size of the leak, and estimates based on experimental data vary widely, ranging from an insignificant fraction to values of over 50 per cent of the stroke volume.

When the general contour of the aortic electrokymographic curves is considered, it is probable that many factors influence their general shape. In some instances the tracings revealed a sharp and abrupt discharge of blood in the early phases of systole (as in fig. 1, *B*), with a rather rapid decline in volume increase in later systole. This rapid ejection of a large volume of blood in early systole is due probably in part to the presence of increased initial tension existing at the onset of systole within the ventricle in patients with aortic insufficiency. However, a second factor which probably explains the rapidity of ejection of blood in early systole, is that ejection begins at a lower intraventricular pressure during systole, owing to the lower diastolic level of aortic pressure in most cases.[9, 10] In other instances (as in fig. 1, *C*) this early abrupt increase in volume was not noted, and the curves rose more slowly and declined in a similar fashion. In this connection it should be recognized that most of the patients were studied in hospital or clinic practice and revealed varying degrees of myocardial insufficiency, which probably influenced the velocity and type of ejection that occurred. Another factor which may determine the shape of such curves, and which Wiggers and Maltby[10] thought to be of great importance in determining aortic pressure patterns, is the type of ventricular contraction exhibited by the ventri-

cle. Thus, in milder degrees of aortic valvular incompetency, the heart contracted usually in an "after loaded" fashion, and the ventricular and aortic pressure curves mounted rapidly and to greatest height in early diastole. In larger aortic regurgitant leaks, however, the ventricular pattern of response was of a "loaded" type with a more gradual slope in ascent and descent, and with the aortic pressure pulse strongly resembling the ventricular curves. This latter explanation may be the fundamental cause of the variations seen in the aortic electrokymograms. However, the possibility of "positional" movements also influencing the shape of these tracings cannot be excluded.

When the data regarding the duration of ejection are considered, although not finally conclusive, they indicate that the period of systole in patients with aortic insufficiency is usually prolonged beyond that of normal subjects. This is probably due to the increased volume of blood which the ventricle must expel. The attendant increased initial tension of the muscle is also probably of great importance in this connection. An increase in the duration of systole has been shown to accompany an increased initial intraventricular tension in experimental studies in animals.[15] Since the initial ventricular tension is elevated in experimental aortic insufficiency, a similar mechanism is probably operative in prolonging the contraction phase in patients with such lesions. The possible effects of myocardial insufficiency in producing such a prolongation cannot be eliminated, however.

The most constant feature of the left ventricular electrokymographic tracings was a tendency to smooth over or eliminate many of the phases of rapid volume change. Thus the rapidly filling phase was not well marked in the majority of tracings of patients with aortic insufficiency. Similarly, even with slow rates the normal plateau of diastasis and the increase in ventricular volume due to auricular contraction were often poorly marked or absent. Although such tracings are admittedly not diagnostic in nature, they appear to be a deviation from the normal pattern. While a sudden marked increase in ventricular volume in early diastole might have been anticipated in large leaks, this finding was not detectable in these tracings. "Positional" movements at the apex of the heart are often marked early in diastole and these may have obscured such a rapid increase in volume in some cases. However, it is more probable that the retention of residual blood in a dilated ventricle plus the early regurgitation of blood from the aorta has produced these alterations. These factors would combine to fill the ventricle to a considerable degree before the onset of rapid filling. In the case of a chamber of greater volume, the increment of a given amount of additional blood from the auricle would produce a smaller change in outward movement of the ventricular wall. There is reason to believe, from experimental work in animals, that the existence of aortic insufficiency, by filling the ventricle in the earliest phase of diastole, actually reduces the amount of blood which enters this chamber in the normal rapid filling phase, which occurs somewhat later.[12] Hence the usual steep outward curve of movement normally seen in the rapid filling phase would be considerably attenuated and its slope diminished, under these conditions. The same factors would tend to obliterate or obscure the normal plateau of diastasis and also the terminal increase in volume due to auricular systole. This explanation appears to be the most feasible one to explain the alterations produced in the ventricular electrokymogram.

In an individual in whom the origin of a diastolic murmur is in doubt, the electrokymogram may be of considerable help in determining whether aortic or pulmonic valvular insufficiency exists. From the constancy with which variations in the electrokymographic tracings were obtained in patients with aortic insufficiency, it is probable that they will become a laboratory aid of corroborative value in the diagnosis of valvular insufficiency of the great vessels. No patient in the present group with definite signs of aortic insufficiency failed to show the characteristic alterations noted above in the aortic electrokymogram. Since

most of these patients manifested clinical signs of moderate to large regurgitant aortic leaks, it is possible that very slight degrees of aortic insufficiency might fail to show such aberrations. It also appears that electrokymographic tracings may be of aid in clarifying the diagnosis of aortic stenosis when systolic murmurs are found at the base of the heart.

Summary

1. Electrokymographic studies of the heart and great vessels were made in 22 patients with clinical signs of aortic insufficiency.

2. Variations from the normal were noted in all patients. These included: (a) A diminution or absence of the normal aortic incisural markings. This was a constant finding in all patients. (b) A rapid decline in volume in early diastole. (c) Alterations in the general shape and contour of the aortic tracings. (d) Prolongation of the duration of ejection (and hence systole) in most patients, compared with normal subjects. (e) Variations in the normal ventricular filling pattern of the left ventricle with a flattening and decrease in the normal changes in gradient in many patients.

3. One patient with pulmonic insufficiency revealed abnormalities of the pulmonic and right ventricular electrokymograms which resembled those seen in association with aortic insufficiency.

4. Two patients with aortic insufficiency complicated by aortic stenosis revealed definite alterations from the normal which are described.

5. The probable factors operative in causing these changes in the electrokymogram, and the diagnostic value of these patterns in patients are discussed.

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A New X-ray Technic for Visualization of the Heart and Great Vessels

By FERDINAND F. MCALLISTER, M.D., AND CLAUD S. BECK, M.D.

A new roentgenographic technic is described, utilizing a balloon fitted over the opening of a cardiac catheter; the latter may then be threaded into the heart chambers via a superficial vessel. Momentary inflation of the balloon with air or a contrast medium outlines the heart chambers for x-ray exposure.

THE RECENT rapid advances in experimental and clinical cardiac surgery require concomitant advances in analytic and diagnostic technic. To aid in the x-ray evaluation of experimentally induced alterations in the heart and great vessels the following technic has been developed.

A No. 6 or No. 8 olive-tipped cardiac catheter is fitted with a balloon over the opening near the tip in the same fashion that a balloon is fitted to a Miller-Abbott tube. The balloon is tested to ascertain that it is air tight and the catheter is sterilized.

The dog (or other animal) to be examined is anesthetized with Nembutal or ether, heparinized, and one of the external jugular veins is exposed aseptically. The balloon is completely deflated and the catheter is introduced into the vein with a rotary motion. The tip may usually be advanced without difficulty into the right ventricle where its arrival is announced by a vigorous pulsating thrust of the catheter. The latter is further advanced until resistance is encountered and a film is exposed to determine the position of the tip. Frequently this will be located in one of the branches of the pulmonary artery or may be so placed by gentle manipulation. If it is desired to visualize this area, the animal is placed in the appropriate position, the balloon is rapidly inflated by means of a syringe with 20 to 30 cc. of air, the x-ray film is exposed, and the balloon is rapidly deflated. By controlled withdrawal of the catheter it is now possible to visualize on additional films the pulmonary artery, the right auricle, and the great veins. The progress of the catheter may be followed throughout fluoroscopically, but this is not essential.

The technic may be varied by introducing a radio-opaque substance into the balloon in place of air. This is particularly useful when the field to be visualized overlies the lung fields and air does not supply sufficient contrast. However, such substances cannot be introduced and aspirated from the balloon as rapidly as air and are more upsetting to the heart. Since air has been used in most of our studies, we have called the x-ray pictures so taken "pneumocardiograms."

When air is used there is usually very slight disturbance of the circulation since the balloon is inflated for only a few seconds. There may be a few extrasystoles, temporary bradycardia, or tachycardia. During the withdrawal of the catheter, the rough edges of attachment of the balloon may get caught temporarily on one of the cordae tendinae of the tricuspid valve but usually may be freed by manipulation of the catheter. In spite of heparinization, small clots occasionally may be found attached to the balloon in its creases and at the rough ends. Because of these latter complications, this technic is not recommended for human subjects until such time as a catheter is designed with a balloon fitted smoothly into the substance of the catheter.

The photographs of x-ray plates presented in figures 1 through 6 demonstrate the possibilities of cardiac and great vessel visualization with this technic.

SUMMARY

A new x-ray technic is described for visualization of the heart and great vessels. Air contrast is obtained by inflation of a balloon attached to a cardiac catheter.

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Aided by a Research Grant from the Division of Surgery, United States Public Health Service.

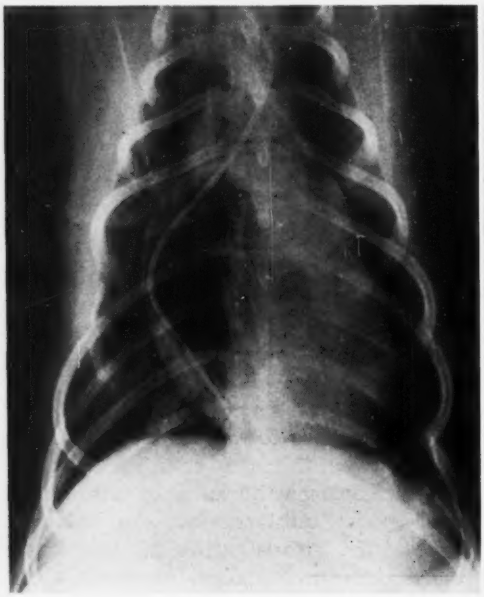

Fig. 1

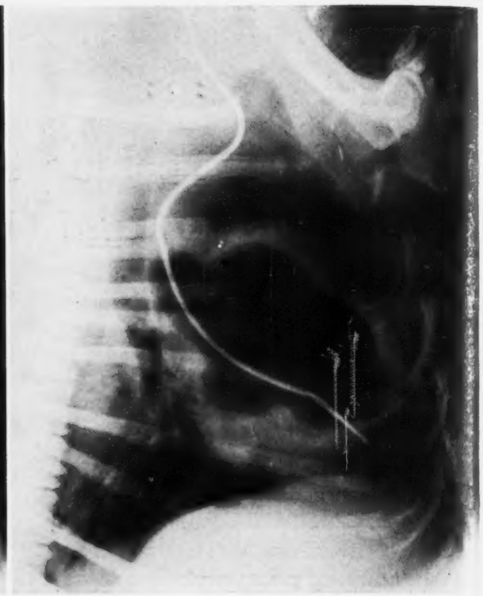

Fig. 2

Fig. 1.—Anteroposterior film of a dog's chest. The catheter has been passed into the right side of the heart and the balloon has been inflated with 40 cc. of air. The right auricle is clearly demonstrated.

Fig. 2.—Right lateral film of the chest of the same dog as shown in figure 1, exposed a few moments later. The tip of the catheter is in the lower portion of the right ventricle. Inflation of the balloon has resulted in outlining the terminal portion of the vena cava, the right auricle, and the major portion of the right ventricle.

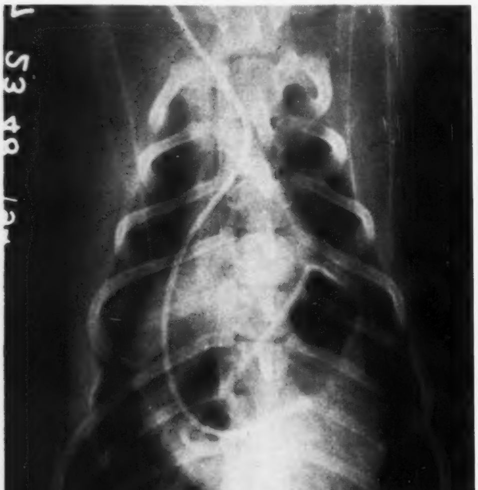

Fig. 3

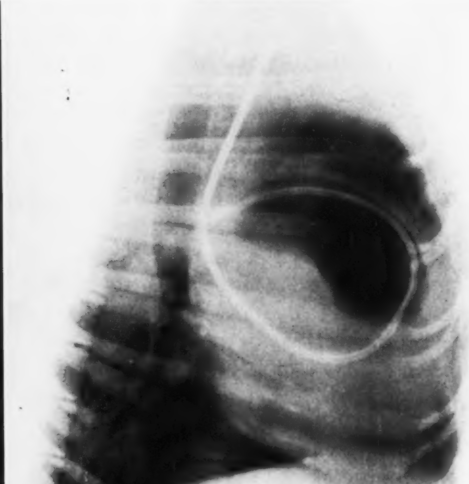

Fig. 4

Fig. 3.—Anteroposterior view of a dog's chest with the tip of the catheter in the pulmonary artery. Inflation of the balloon has outlined the pulmonary artery, conus, and right ventricle.

Fig. 4.—Right lateral film of a dog's chest with the tip of the catheter at the bifurcation of the pulmonary artery. The inflated balloon outlines the pulmonary artery.

FIG. 5

FIG. 6

FIG. 5.—Right lateral film of a dog's chest with the catheter tip in a branch of the left pulmonary artery. The balloon has been distended with 30 cc. of lipiodol and the bifurcation of the pulmonary artery is demonstrated.

FIG. 6.—Right lateral film of the chest of a dog whose pulmonary artery had been constricted to the caliber of a lead pencil by means of an umbilical tape tie one week previously. The tip of the catheter would not pass through the constriction, but when the catheter buckled, a loop containing part of the balloon slipped through the narrowing. Inflation of the balloon has outlined the constriction.

Increasing Congestive Heart Failure: A Manifestation of Digitalis Toxicity

By Robert C. Batterman, M.D., and Leonard B. Gutner, M.D.

While it has been widely appreciated that myocardial function is increased with optimal digitalis dosage, it is not well recognized that toxic concentration may impair myocardial efficiency to the point of producing increased signs and symptoms of congestive heart failure. This was demonstrated in 15 patients who could be adequately maintained with a digitalis preparation. Upon increase in dosage, all patients presented an increase in congestive heart failure which subsided upon stopping or decreasing the digitalis dosage.

IN THE treatment of chronic congestive heart failure an attempt is made to establish the optimum maintenance dose of digitalis or any of the cardiac glycosides in order to achieve the maximum possible muscular efficiency of heart muscle. It is well recognized that a patient not receiving sufficient digitalis will manifest varying degrees of impaired cardiac reserve. On the other hand, it has not been appreciated that overdosage of digitalis may also result in lessened myocardial efficiency. It is the purpose of this report to present evidence that congestive heart failure may occur secondary to digitalis intoxication.

During our studies[1] on the evaluation of digitalis-leaf preparations and the various glycosides for the management of the ambulatory patient with congestive heart failure this phenomenon brought itself to our attention. In every patient we attempted to determine for each individual glycoside and digitalis-leaf preparation the therapeutic range. This consisted of first ascertaining the minimal daily dose for satisfactory maintenance and then, at eight- to twelve-week intervals, increasing by small increments the daily dose of the preparation being investigated until the earliest detectable signs and symptoms of toxicity supervened.

A total of 93 patients was included in this study. None of these patients manifested any of the signs or symptoms of congestive heart failure when the optimum dose of a digitalis preparation was administered; and furthermore, as long as this optimum dose was continued, none required any diuretic agent or other adjuvant therapy. All of the patients were unrestricted as to diet throughout the period of observation. None of the patients presented any evidence of a complication of their heart disease such as rheumatic activity, myocardial infarction, or any other precipitating factor which could possibly have accounted for the noted decreased efficiency of heart muscle.

During this investigation, we had the opportunity to evaluate various lots of digitalis leaf, digoxin, digitoxin, lanatoside C, urginin maritima, urginin indica, and gitalin. In this group of 93 patients there were 235 manifestations of minimal toxicity. Fifteen of these patients presented sixteen episodes of increasing signs and symptoms of congestive heart failure when the dose level of the digitalis preparation in question reached the toxic range. Every patient exhibited, in addition to the syndrome of congestive failure, one or more of the accepted manifestations of digitalis intoxication, such as anorexia, nausea, vomiting, epigastric distress and pain, visual disturbances, headache, vertigo, precordial pain, palpitations, lethargy, fatigue, weakness, nervousness, neuralgias, insomnia, and premature systoles.

It must be emphasized that these patients were entirely free of any manifest signs or symptoms of congestive heart failure when being maintained on their optimum dose of a

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digitalis preparation; and that following the toxic episode, when the particular preparation was completely discontinued or reduced to optimum or suboptimum levels, the various signs and symptoms of congestive heart failure subsided along with the other well-known evidences of digitalis toxicity.

A summary of the protocols of these fifteen patients is presented in table 1. Case histories of several of them are given in greater detail below.

Case Histories

Case 2.—K. C. is a 55 year old white single woman who first noted the onset of diminished cardiac reserve in 1943 with the gradual occurrence of dyspnea and fatigue. Since that time digitalis preparations had been prescribed irregularly. In September, 1947, the patient developed edema of the legs and entered Bellevue Hospital where the diagnosis of arteriosclerotic heart disease with cardiac enlargement and auricular fibrillation was made. At that time, all attempts to arrive at the cause of the hepatosplenomegaly which was present failed and it was classed as undetermined. Since that hospitalization, she has been successfully maintained without manifest signs of congestive heart failure on an ambulatory status on 0.1 Gm. of digitalis leaf or an equivalent dose of a glycoside. On February 5, 1948, after having taken 0.2 Gm. of digitalis leaf for the previous five weeks, she presented herself at the clinic with marked weakness, increased lethargy, and fatigue. The ventricular rate was 52 beats per minute with runs of coupled rhythm. There were also dyspnea, bilateral basal moist râles, and minimal pretibial edema, which were not present previously. Digitalis was withheld for three days and then the patient was instructed to take 0.1 Gm. daily. At the end of three weeks, during which period the patient remained ambulatory, there was much less dyspnea and weakness, the lungs were clear and the legs free of edema, and the weight had dropped six pounds. The electrocardiogram revealed an occasional ventricular premature systole.

Case 6. N. T. is a 48 year old married white woman with a history of acute polyarthritis in 1920 at the age of 20 years. When she first came under our observation in 1940, physical examination revealed systolic and diastolic murmurs both at the apex and base, a systolic thrill at the aortic area, a pulsating liver, and a totally irregular rhythm; fluoroscopy gave evidence of generalized cardiac chamber enlargement. The diagnosis was made of rheumatic heart disease, enlarged heart with mitral and aortic insufficiency and stenosis, tricuspid insufficiency, and auricular fibrillation. Digitalis therapy was instituted because of the onset of dyspnea, orthopnea, fatigue, edema, and palpitations, and was by itself sufficient to maintain the patient in good compensation. On September 16, 1941, the patient came to the clinic, having taken 0.1 and 0.2 Gm. of digitalis leaf on alternate days for the previous three weeks, complaining of insomnia, increased dyspnea, and edema. A weight gain of 7½ pounds was noted. Because the dose of digitalis was thought to be inadequate, she was placed on 0.2 Gm. of digitalis leaf daily and instructed to return to the clinic in three weeks and to remain ambulant. However, she presented herself one week later with anorexia, nausea, vomiting, visual disturbances, insomnia, palpitations, progressive dyspnea and edema, and signs of minimal ascites and an enlarging liver. Digitalis was stopped for three days and then 0.1 Gm. prescribed daily. One week later the signs of toxicity had disappeared and those of congestive failure were markedly improved. There was also a 5¼-pound weight loss. A subsequent second trial on 0.1 and 0.2 Gm. on alternate days produced anorexia, nausea, vomiting, yellow vision, palpitations, precordial pain, and weight gain after ten days' administration. This proved that this last dosage was definitely in the toxic range for this patient.

Case 12. L. S. is a 48 year old white married man; diagnosis, an unknown type of heart disease and hyperthyroidism with cardiac enlargement, dilatation of the aorta, and auricular fibrillation. In 1933 he first complained of nervousness, tremors, sweating, weakness, and muscle pains. Between 1931 and 1939 he noted the onset of progressive palpitations, tachycardia, dyspnea, orthopnea, and peripheral edema, and was treated with digitalis preparations and Lugol's solution. In August 1940, he was hospitalized for a subarachnoid hemorrhage, from which there was complete recovery except for a residual ptosis of the left eyelid. The patient was maintained without manifest signs and symptoms of diminished cardiac reserve on 0.1 Gm. of digitalis leaf or an equivalent dose of a glycoside. On November 17, 1942, eight weeks after being placed on 0.2 Gm. of digitalis leaf daily, he came to clinic with anorexia, nausea, weakness, fatigue, lack of vigor, insomnia, cloudy vision, precordial aching, increasing dyspnea, orthopnea and edema, nocturia, and a ventricular rate of 42 beats per minute. Digitalis was withheld for one week and then 0.1 Gm. administered daily for two weeks, during which interval the patient remained ambulatory. At the end of this time, all the signs of toxicity and congestive heart failure cleared and a weight loss of 4 pounds was noted. The patient was subsequently well maintained.

TABLE 1.—*Summary of Patients Presenting Increasing Congestive Heart Failure With Toxic Doses of Various Digitalis Preparations*

Case No., Patient, Sex, Age	Cardiac Diagnosis*	Digitalis Preparation	Daily Maintenance Dose	Daily Toxic Dose	Weeks Needed to Produce Toxicity	Toxic Symptoms	Evidence of Increased Failure	Subsequent Course	Remarks
1, N. C., F, 79	Arteriosclerosis and hypertension. Enlarged heart, coronary sclerosis, myocardial fibrosis. Auricular fibrillation	Digitalis leaf	0.1 Gm.	0.1 and 0.2 Gm. on alternate days	3	Anorexia, eyeball pain, blurred vision, nervousness, lower extremity neuralgias	Edema, dyspnea	Symptoms cleared on withholding digitalis for 2 weeks	
2 K. C., F, 54	Arteriosclerosis. Enlarged heart, coronary sclerosis, myocardial fibrosis. Auricular fibrillation	Digitalis leaf	0.1 Gm.	0.2 Gm.	5	Nausea, headache, fatigue	Râles, enlarged liver, trace of edema	Cleared after no drug for 3 days, then 0.1 Gm. O.D. with 6-lb. weight loss	
3 M. W., F, 53	Rheumatic fever—inactive. Enlarged heart, mitral insufficiency, mitral stenosis. Normal sinus rhythm	Digitoxin	0.1 mg.	0.2 mg.	4	Prolonged P-R interval, dropped beats	Increased ankle edema	Responded with decreased edema and weight loss to no drug for 2 weeks	
4, M. K., M, 54	(1) Arteriosclerosis. Coronary sclerosis, myocardial fibrosis. Auricular fibrillation. (2) Lung cyst	Digitalis leaf	0.1 Gm.	0.2 Gm.	3	Unsteady on feet, weakness, occasional ventricular premature systoles	Edema, enlarged liver	Decreased edema and hepatomegaly and weight loss after no drug for 2 days; then, 0.1 Gm. O.D.	

5, H. F., M 82	Arteriosclerosis. Enlarged heart, coronary sclerosis, myocardial fibrosis. Auricular fibrillation	Digitoxin	0.5 mg.	0.6 mg.	16	Anorexia, epigastric pain, nausea, fatigue, weakness, "spots" in eyes	Marked edema, basal râles, nocturia	Disappearance of râles and withholding digitoxin	
6, N. T., F, 48	Rheumatic fever—inactive. Enlarged heart, mitral insufficiency and stenosis, tricuspid insufficiency, aortic insufficiency, and stenosis. Auricular fibrillation	Digitalis leaf	0.1 Gm.	0.1 and 0.2 Gm. on alternate days	3	Palpitations, insomnia, fatigue, visual disturbances	Edema, dyspnea, 7½-lb. weight gain, enlarging liver	Improved on reduction to 0.1 Gm. O.D.	A second trial of 0.1 Gm. and 0.2 Gm. alternately for 10 days produced anorexia, nausea, vomiting, yellow vision, palpitations, precordial pain, and 5-lb. weight gain.
7, J. S., F, 47	Rheumatic fever—inactive. Enlarged heart, mitral stenosis and insufficiency, aortic insufficiency. Auricular fibrillation	Gitalin	0.75 mg.	1.25 mg.	7	Toothache, visual "spots", ventricular premature systoles	Edema, enlarging liver	On Gitalin 0.5 mg. O.D. lost edema and 8¼ lbs. in weight, and liver receded	
8, P. R., M, 65	Syphilis and arteriosclerosis. Enlarged heart, aortitis, dilated aorta, aortic insufficiency, coronary sclerosis, myocardial fibrosis. Auricular fibrillation	Digitalis leaf	0.1 Gm.	0.1 and 0.2 Gm. on alternate days	3	Nausea, vomiting, vertigo	12-lb. weight gain	Sent to hospital but follow-up not valid because patient given intravenous Mercuzanthin on admission	

* According to Nomenclature and Criteria for Diagnosis of Diseases of the Heart (New York Heart A., 1939).

TABLE 1.—*Continued*

Case No., Patient, Sex, Age	Cardiac Diagnosis*	Digitalis Preparation	Daily Maintenance Dose	Daily Toxic Dose	Weeks Needed to Produce Toxicity	Toxic Symptoms	Evidence of Increased Failure	Subsequent Course	Remarks
9, J. H., M, 57	Unknown (rheumatic type). Enlarged heart, mitral insufficiency and stenosis. Auricular fibrillation	Gitalin	0.75 mg.	2.25 mg.	2	Right supraorbital headache, palpitations, precordial pain, blurred vision	Edema	Improved on 0.75 mg. Gitalin O.D. with loss of edema	
10, W. D., M, 70	Arteriosclerosis. Enlarged heart, coronary sclerosis, myocardial fibrosis. Auricular fibrillation	Lanatoside C	1.0 mg.	2.0 mg.	8	Anorexia, visual disturbances, complete heart block (ECG)	Bilateral moist râles, marked edema, enlarging liver	Hospitalized and given lanatoside C (1.0 mg., B.I.D.) with 24-lb. weight loss, loss of edema, and recession of liver	Division of dose equivalent to decreasing dose[1]
		Lanatoside C	1.0 mg.	2.5 mg.	13	Anorexia, insomnia, vertigo, nervousness, poor vision, occasional headaches, palpitations	Dyspnea, edema, basal râles, cough, fatigue, weakness	No drug for 1 week; then on reduced dosage lost 11 lbs. and almost all edema, râles, cough	
11, F. J., M, 85	Unknown—Arteriosclerosis. Enlarged heart, myocardial fibrosis. Auricular fibrillation	Urginin maritima	0.5 mg.	2.0 mg.	10	Vertigo, diplopia	Râles, enlarged liver	Improved on Digoxin, 0.5 mg. O.D.	Dose of digoxin equivalent to 0.5 mg. Urginin maritima

12, L. S., M, 52	Unknown and hyperthyroidism. Enlarged heart dilated aorta. Auricular fibrillation	Digitalis leaf	0.1 Gm.	0.2 Gm.	7	Anorexia, nausea, weakness, fatigue, lethargy, sleepiness, multiple premature systoles, heavy precordial aching, nervousness	Edema, dyspnea, nocturia	At end of 3 weeks (1 week without digitalis and 2 weeks on 0.1 Gm. O.D.) signs of failure completely disappeared	
13, M. C., F, 59	Rheumatic fever—inactive. Enlarged heart, mitral insufficiency and stenosis, aortic insufficiency. Normal sinus rhythm	Digitalis leaf	0.1 Gm.	0.1 and 0.2 Gm. on alternate days	13	Nausea, anorexia	Edema, enlarged liver	Signs of failure cleared on reduction to 0.1 Gm. every other day	
14, C. M., F, 54	(1) Rheumatic fever—inactive. Enlarged heart, mitral insufficiency and stenosis, aortic insufficiency. Auricular fibrillation. (2) Essential hypertension	Lanatoside C	0.5 mg.	1.0 mg.	6	Anorexia	12-lb. weight gain, râles, dyspnea, orthopnea, increased hepatomegaly, ascites, marked edema	At end of 1 week on Lanatoside C (0.5 mg. B. I. D.) there was $3\frac{1}{2}$-lb. weight loss, less dyspnea and orthopnea, and râles had disappeared	Division of dose equivalent to decreasing dose[1]
15, H. W., M, 51	Unknown. Enlarged heart. Auricular fibrillation	Gitalin	0.5 mg.	0.5 and 0.75 mg. on alternate days	3	Anorexia, nausea, vomiting, headache, blurred vision, weakness, coupled rhythm	Increased dyspnea and orthopnea, $2\frac{1}{2}$-lb. weight gain	After no drug for 1 week, then 0.1 Gm. digitalis leaf every 2 days for 3 weeks, 5-lb. weight loss, much less dyspnea and fatigue, no orthopnea	

Discussion

Regardless of the mechanism for congestive heart failure, whether forward or backward, all investigators are in accord that the fundamental defect is one of impaired muscular efficiency of the heart with the consequent decrease in the amount of work which it is capable of performing. Furthermore, although the exact mode of action of digitalis and its preparations for improving congestive heart failure has not yet been established, there is pharmacologic as well as clinical evidence which would indicate that a direct effect on cardiac muscle plays a role in digitalis action. Such evidence is seen in the increased efficiency of the papillary muscle of the cat. Cattell and Gold[2] stimulated the isolated muscle before and after the application of ouabain and digitoxin in concentrations which were comparable to therapeutic doses in man, and noted an increase in the systolic force of contraction. Kabat and Visscher[3] in their study on the influence of K-strophanthosid upon the tortoise ventricle showed that the work capacity of the myocardium was increased with optimal glycoside levels. This was primarily an effect upon contractility and unrelated to so-called muscular elasticity or tonus. Observations in the failing heart-lung preparation and in patients in congestive heart failure have demonstrated an increased cardiac output following digitalis administration, which increase is presumably largely due to an enhanced contractility, although many variables affecting cardiac output are also involved.

Experimental evidence either in the animal or the clinical use of digitalis preparations would indicate that the maximum efficiency of heart muscle function is related to optimum dosage which must be determined specifically for each experimental procedure or individual patient. Exceeding this optimum dosage results in a progressive decrease in myocardial efficiency which can be interpreted as representing a toxic influence of digitalis or its various preparations. Thus, Cattell and Gold[2] and Kabat and Visscher[3] found that when this optimum concentration was surpassed and toxic ranges entered, the contractility of the papillary muscle and tortoise ventricle, respectively, decreased and the work done was reduced.

Although this phenomenon was not appreciated clinically heretofore, several investigators reported observations which could be interpreted as clinical evidence of impaired myocardial efficiency. Thus, Mackenzie[4] and Windle[5] each reported 2 patients in whom pulsus alternans, a sign of disturbed myocardial contractility, occurred during the administration of a digitalis preparation. Except for one of Mackenzie's patients, the remaining 3 patients received toxic doses of the tincture of digitalis and presented pulsus alternans associated with other signs and symptoms of overdosage. It is of interest that one of Windle's patients was a 35 year old woman with functional heart disease without cardiac enlargement. However, the fact that frank signs and symptoms of congestive heart failure could be produced by overdosage of digitalis products was not readily appreciated. Our study would indicate that above the optimum dose required for proper digitalization the patient, in addition to exhibiting the classical manifestations of digitalis intoxication, may present increasing signs and symptoms of congestive heart failure. Although none of the patients in this report presented congestive failure as the only indication of digitalis toxicity, there is no correlation between the severity of the classic toxic signs and the advent of impaired myocardial efficiency. In other words, it is conceivable on a purely pharmacologic basis where all the effects of digitalis upon cardiac physiologic functions may be independent of one another, that in some patients this effect upon contractility may be the predominant action. In this situation, congestive heart failure might occur in the absence of the other well-accepted evidences of toxicity.

On an experimental basis in these 15 ambulatory patients, there was no difficulty in demonstrating that congestive heart failure occurred with digitalis toxicity. In all cases, elimination or reduction in dosage of the digitalis preparation resulted in an improvement in myocardial efficiency with subsequent satisfactory maintenance without signs and symptoms of diminished cardiac reserve. However,

patients frequently first come under observation in severe congestive failure in whom there is a history of having taken a dose of a digitalis preparation which on the basis of predictability would be a toxic dose. Clear-cut evidence of digitalis intoxication is not available in these patients since vague gastrointestinal symptoms may be related either to visceral congestion or to toxicity. It is our feeling that many of these patients are truly toxic and that the rational regimen of therapy should be to discontinue digitalis and the patient evaluated further on bed rest alone before instituting other therapeutic measures.

Summary

Fifteen patients presenting sixteen episodes of increasing congestive heart failure as a manifestation of digitalis toxicity are reported.

It is believed that the syndrome of congestive heart failure as a toxic sign is the result of a direct muscular action with the consequent decrease in myocardial efficiency.

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Acute Myocarditis with Bundle Branch Block due to Sulfonamide Sensitivity

By Alfred Lilienfeld, M.D., Elliot Hochstein, M.D., and William Weiss, M.D.

This is a case report of a patient who developed generalized manifestations of sulfonamide sensitivity, with evidence of involvement of the skin, mucous membrane, central nervous system, liver, and myocardium. Special attention is directed to the myocardial involvement, and particularly to the development of bundle branch block. The changes were reversible and complete recovery ensued.

THE CLINICAL manifestations of sulfonamide sensitivity are well recognized. The effects on the cardiovascular system, however, have only recently been receiving the attention they deserve.[1, 2] The following case is presented because of the striking clinical and electrocardiographic evidence of involvement of the myocardium in association with other manifestations of sensitivity.

Case Report

The patient was a 24 year old laundress. Her past history was irrelevant. At the age of 18 she was treated for an infected finger, but a history of specific medication was not obtained. In February 1948 she developed a sore throat with fever, for which she was given sulfathiazole and sulfadiazine. Within four hours after the second dose she developed vomiting, diarrhea and abdominal cramps, and her face became swollen. These symptoms subsided in a week.

One week before she was admitted to the hospital she again developed a sore throat with fever. She was treated with sulfadiazine for five days despite the onset of abdominal cramps and diarrhea, facial edema, and confusion, immediately following the first dose. The symptoms became progressively worse and the patient was admitted to the hospital on June 14, 1948.

Examination showed a toxic, disoriented woman who was dyspneic and orthopneic. Her rectal temperature was 103.5 F. Her face was markedly swollen, and there was an erythematous, scaly rash over the bridge of her nose and over her cheeks. There were white patches on the buccal mucosa and the lingual tonsil. The soft palate was edematous. The conjunctivae were congested; the pupils and fundi were normal. The ears and nose were normal. The heart was not enlarged on percussion. The rate was rapid but regular; the sounds were distant at the apex, and the second pulmonic sound was louder than the second aortic sound. There was a presystolic gallop at the apex and a Grade 2 systolic murmur at the pulmonic area. The blood pressure was 80/70. The lungs were clear. Abdominal, rectal, and pelvic examinations revealed no abnormality. There was an equivocal Babinski reflex on the right and a positive Oppenheim reaction, and exaggerated knee jerk on the left.

On admission, the red blood cells numbered 6,000,000 per cu.mm. of blood; the hemoglobin value was 14.4 grams; there were 17,800 white blood cells per cu.mm. with 89 per cent polymorphonuclear neutrophils, of which 30 per cent were band forms; the urine was normal. A throat culture for diphtheria was negative. The blood sugar was 135 mg. per 100 cc. of blood; whole blood chlorides were 456 mg. per 100 cc.; the carbon-dioxide combining power was 56 volumes per cent; and the blood urea nitrogen was 37.8 mg. per 100 cubic centimeters. The test for sickling was negative. Serologic blood tests for syphilis were negative. The icterus index was 6.0.

Course. For the first two days the patient's condition was essentially unchanged. On the third day she went into peripheral vascular collapse, the blood pressure falling to 60/30. Five hundred cc. of plasma were administered with a rapid effect. From this time on there was a gradual improvement. The temperature, which had varied between 103.6 and 104.6 F., gradually returned to normal in two weeks. The patient became mentally alert at the end of the first week. The edema of the soft palate, the swelling of the tonsils, and the exudate on the tonsil and buccal mucosa subsided within the week. The swelling of the face and the rash disappeared by the second week. The dyspnea and orthopnea and the gallop rhythm disappeared by the end of the first week. The blood pressure rose during the second week from 100/65 to 135/100 and stabilized at 115/95.

The pathologic reflexes noted on admission were not elicited after the third day. The spinal fluid on this day showed a normal pressure; it contained 35 polymorphonuclear neutrophils per cu.mm., 82 mg.

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of protein per 100 cc., and 647 mg. of chlorides per 100 cc.; the colloidal gold curve read 23333000. On the fifth day there were 5 monocytes per cu.mm. of fluid and the protein content was 121 mg. per 100 cubic centimeters. On the tenth day the protein content was 65 mg. per 100 cc. of fluid and there were no cells present. The spinal fluid Wassermann reaction was anticomplementary.

Serial hemograms showed a reduction in red blood cells to 4,000,000 per cu.mm. of blood and hemoglobin of 14 grams. The white blood cells fell from 17,800 to 10,100 per cu. mm. on the third day and varied around 5,500 thereafter on numerous counts. The differential count reverted to 70 per cent neutrophils, of which 16 per cent were band forms; there were 38 per cent lymphocytes; there were never any eosinophils present on numerous blood counts.

The erythrocyte sedimentation rate on June 23, 1948, was 10 and on July 8, 1948, it was 7 mm. per hour. Urine specimens after the initial normal findings varied in specific gravity between 1.010 and 1.020; a trace of albumin was noted in all specimens, and on two occasions only the microscopic examination showed a few white blood cells and a few hyaline and granular casts.

A blood sulfadiazine level was 6.8 mg. on the morning of the third hospital day (June 16), forty-eight hours after the last dose of the drug. On June 22, sulfadiazine was no longer present in the blood. The blood urea nitrogen fell to 14 mg. per 100 cc. on June 22. The blood serum proteins were 6.8 grams per 100 cc., with albumin value of 4 grams and globulin of 2.8 grams.

At the end of the first week (June 21) the reaction to the cephalin flocculation test was 4+ and on June 28 it was negative.

X-ray examination of the chest, performed on June 15 and June 23, by aid of the portable machine and taken with the patient in the supine position, showed no evidence of involvement of the lungs. The heart size could not be properly evaluated because of the technic employed. A 6-foot plate exposed on July 6 showed the heart to be of normal size and configuration.

Electrocardiograms made on the third day and at frequent intervals thereafter showed definite evidence of an active myocardial process (fig. 1). On June 16, there was evidence of intraventricular conduction defect with marked left-axis deviation. On June 18, the conduction defect had progressed and now assumed the pattern of a right bundle branch block. On June 23, the conduction defect had regressed, the duration of the QRS complex coming well within normal limits, but there were indications of myocardial involvement in the RS–T segments and slightly inverted T waves in Leads I and II. The T wave in Lead III was isoelectric and T waves in Leads CF_4 and CF_5 were low. On June 28 the T wave changes in these leads were more pronounced, becoming more deeply inverted in Leads I and II, slightly inverted in Leads III and CF_5, and shallow and diphasic in Lead CF_4. The T wave in Lead CF_2 was higher and more peaked.

On July 2, the tracing showed minimal comparative changes; the upward convexity of the RS–T segment in Lead II was less evident and the diphasic character of the T wave in Lead CF_4 was somewhat clearer, while the T wave in Lead CF_5 was slightly more inverted. On July 8, the first evidences of regression were noted. The T wave in Lead I became upright, in Lead II it was less deeply inverted, in Lead CF_4 it was upright, and in Lead CF_5 it became isoelectric. On July 23, the tendency toward improvement was maintained, the T wave in Lead I becoming higher, diphasic in Lead II, lower in CF_4, and slightly higher in Lead CF_5.

On August 6, 1948, the tracing showed no essential comparative changes. The character of the T waves in Leads II, CF_4, and CF_5, however, still indicated some myocardial involvement. The patient was discharged from the hospital after four weeks' stay. A follow-up examination in the clinic four weeks later indicated that there were no symptoms, and the physical findings were normal.

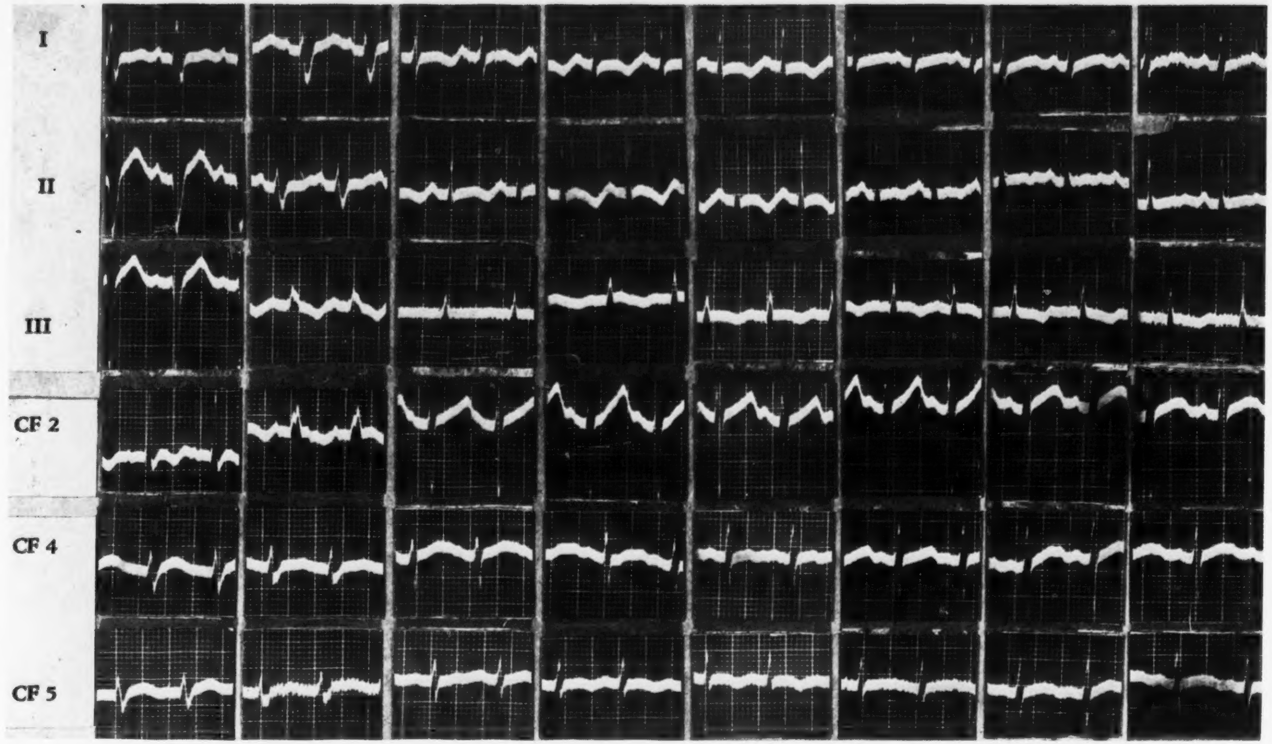
Discussion

The patient presented the clinical picture of an acute infection with marked toxicity. There was evidence of involvement of the skin, mucous membrane of the oral cavity and pharynx, the central nervous system, and the gastrointestinal and cardiovascular systems. The widespread character of this involvement suggested an etiologic factor other than the infection for which she was originally given chemotherapy. The possibility of diphtheria, scarlet fever, agranulocytosis, and pulmonary infections with sepsis which could produce such a picture was excluded on clinical and laboratory grounds. The probability of sulfonamide hypersensitivity was suggested by the history of her previous reaction in February 1948 to the administration of sulfonamides which caused immediate vomiting, abdominal cramps and diarrhea, and swelling of the face.

The criteria for the diagnosis of drug sensitivity are[3, 4]:

1. A history of initial use of the drug without untoward reaction. This constitutes the sensitizing dose.

2. The subsequent dose after sensitization need not be excessive, and the reaction bears no relationship to the magnitude of the dose.



A—June 16 *B*—June 18 *C*—June 23 *D*—June 28 *E*—July 2 *F*—July 8 *G*—July 23 *H*—Aug. 6

FIG. 1: *A*, Sinus tachycardia, marked left-axis deviation, intraventricular conduction defect. QRS duration 0.11 second. *B*, Right bundle branch block, right-axis deviation, deep S_1, upright QRS_3, and notched QRS in Lead CF_2. *C*, Disappearance of bundle branch block, QRS of 0.06 second's duration, RS-T_1 and RS-T_2 slightly convex upward, inversion of T waves in Leads I and II, low T waves in Leads CF_4 and CF_5. *D*, Progression of myocardial damage, further inversion of T_1 and T_2, slight inversion in Leads III and CF_5, T shallow and diphasic in CF_4 and higher and more peaked in CF_2. *E*, Minimal comparative changes; upward convexity of RS-T in Lead II less evident, T in CF_5 slightly more inverted. *F*, First evidences of regression; T_1 upright, T_2 less deeply inverted, and T in CF_5 isoelectric. *G*, Further regression; T_1 higher, T_2 diphasic, T in CF_4 lower and less peaked, T in CF_5 slightly higher. *H*, No essential comparative changes; residual T-wave abnormalities (see text).

3. The reaction does not resemble the pharmacologic or toxic effects of the drug, but assumes one of the following forms: (*a*) Symptoms usually associated with allergy and as such more easily recognizable, e.g., asthma, urticaria, and angioedema. (*b*) Symptoms resembling serum sickness. (*c*) Syndromes suggesting infectious disease, e.g., fever, a variety of rashes, hepatitis, agranulocytosis, thrombocytopenia; central nervous system involvement; hepatitis; and myocarditis.

4. Immunologic criteria. Antibody mechanisms are demonstrable in protein sensitization but not in the case of sensitization due to drugs of a crystalloid nature.

5. Persistence of symptoms as long as the drug is continued.

With regard to the present case, a diagnosis of drug sensitivity is postulated according to the criteria enumerated. The initial sensitization may either have occurred in 1942 at the time the patient was treated for an infected finger or may have resulted from the use of proprietary sulfonamides. Subsequent administration of but one dose of sulfonamides in February 1948 produced almost immediate acute gastrointestinal symptoms and swelling of the face. A repetition of a single dose of sulfonamides at the onset of the present illness again produced immediate gastrointestinal symptoms, followed by disorientation. Despite this, sulfadiazine was given for a week with the development of fever, rash, and mucosal involvement; the central nervous system effects were disorientation, elevated spinal fluid protein, and pathologic reflexes. A 4+ reaction to the cephalin flocculation test was indicative of involvement of the liver. The myocardial involvement which was outstanding was attested to by the dyspnea and orthopnea, gallop rhythm, accentuation of the pulmonic second sound, tachycardia, and the marked electrocardiographic changes. The bundle branch block in particular is stressed because of its rarity in the cases of sulfonamide sensitivity which have been reported.[5, 6, 7]

The validity of the clinical diagnosis of myocardial involvement due to sulfonamide sensitivity is supported by experimental and pathologic studies. In experimental sensitization, Rich and Gregory[8] and others have shown widespread foci of parenchymatous and collagen degeneration with monocytic infiltration and arterial lesions resembling those of periarteritis nodosa. Similar lesions have been reported in patients dying during or after sulfonamide therapy. Rich and Gregory particularly emphasized the presence of the arterial lesions showing hyaline and fibrinoid degeneration of the media with perivascular infiltration of mononuclear and polymorphonuclear cells including eosinophils.

Goodman,[9] in January 1948, reported a case of sulfonamide sensitivity with myocardial involvement in which a muscle biopsy showed the lesions of periarteritis nodosa.

Immunologic confirmation of the diagnosis of sulfonamide sensitivity was not obtained. This is the usual situation in the case of crystalloid drugs.

Summary and Conclusion

A case has been presented with evidence of reversible damage to the following: skin, mucous membrane, central nervous system, liver, and myocardium.

The history and clinical picture fulfill the criteria for the diagnosis of sulfonamide sensitivity. Immunologic studies gave normal findings as they usually do in the case of crystalloid drugs.

The involvement of the myocardium is stressed, and attention is especially directed to the unusual development of bundle branch block.

Sulfonamide sensitivity should be added to the list of causes of myocarditis, and should be considered in any case of myocarditis of obscure nature.

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Cardiac Tamponade Associated with the Administration of Dicumarol

By Charles L. Leedham, Colonel, MC, U.S.A. and James A. Orbison, Major, MC, U.S.A.

The case history is presented of a man 22 years of age who developed cardiac tamponade in association with anticoagulant therapy and nonpenetrating trauma of the heart. Included is a commentary on the delayed appearance of signs indicative of pericardial and/or myocardial damage following severe trauma and the value of serial electrocardiographic observations in the diagnosis thereof. The importance of interpretation of the results of prothrombin testing is discussed and comparative data are presented which indicate the desirability for standardization of methods employed in reporting prothrombin values when used to control anticoagulant therapy with dicumarol.

THE OCCURRENCE of hemorrhagic episodes during the course of anticoagulant prophylaxis or therapy with dicumarol is well known. Although the danger of hemorrhage has been emphasized repeatedly, it is generally considered that the risk of significant bleeding incident to the use of dicumarol is relatively small when a standardized plan of controlled dosage is followed and the accepted precautions are observed. Major bleeding during dicumarol therapy has been encountered, in most series, in less than 2 per cent of cases.[1-5] Although hemorrhage, even of serious proportions, has generally been controllable by the parenteral administration of vitamin K in adequate dosage and fresh whole blood transfusions,[1] lyophilized plasma,[6] or vitamin K_1 oxide,[7, 8] deaths have occurred.[1, 2, 4, 9, 10] On the basis of study of numerous reports, Wright[11] believes that the analysis of fatal cases will usually reveal an associated overdosage of the drug, inadequate laboratory control, or a hemorrhagic site, such as a duodenal ulcer, which is unrelated in its origin to anticoagulant therapy but which presents an added and too often unconsidered risk.

The common sites of bleeding associated with dicumarol administration have been well noted in the literature.[1, 4, 12-14] The more unusual forms of serious bleeding which have been reported include hemoptyses,[15] subarachnoid bleeding,[16] extensive hemorrhage into the brain,[9, 10] bloody pulmonary edema,[17] and hemorrhage into the peritoneal cavity[18] and pleural space.[19] In our review of the literature, no instance of hemopericardium without rupture of the heart could be discovered which had occurred in association with anticoagulant therapy. Because of the inherent danger associated with such an event, it is considered important to point out that this complication can occur, and to record a case of cardiac tamponade associated with, and probably resulting from, the administration of dicumarol.

From the Medical Service, Oliver General Hospital, Augusta, Ga.

Case Report*

A white male veteran, 22 years of age, was admitted to an Army General Hospital as an emergency case on December 23, 1947. The patient had crashed in a small plane from a low altitude and had been thrown against the stick and windshield. Initial examination revealed evidence of severe shock, cerebral concussion or contusion, and multiple compound fractures. Probable involvement of the urinary tract was indicated by gross hematuria. There was evidence of severe vascular injury to the right lower leg, and the right foot was ischemic. There was no visible evidence of injury to the chest. Following emergency shock therapy, reduction and immobilization of the fractures were carried out.

After a rather stormy course for three days, the patient's condition became satisfactorily stabilized except for persistent ischemia of the right foot which was unresponsive to treatment.

During the evening of the eighth day, December 30, 1947, the patient began to complain of sharp pain in the left chest and mild shortness of breath. On examination, blood pressure was 130/80, the

*The assistance of Lt. Col. Edward Cleve and Capt. Simone Brocato in the handling of this case and the assembling of data reported herein is acknowledged.

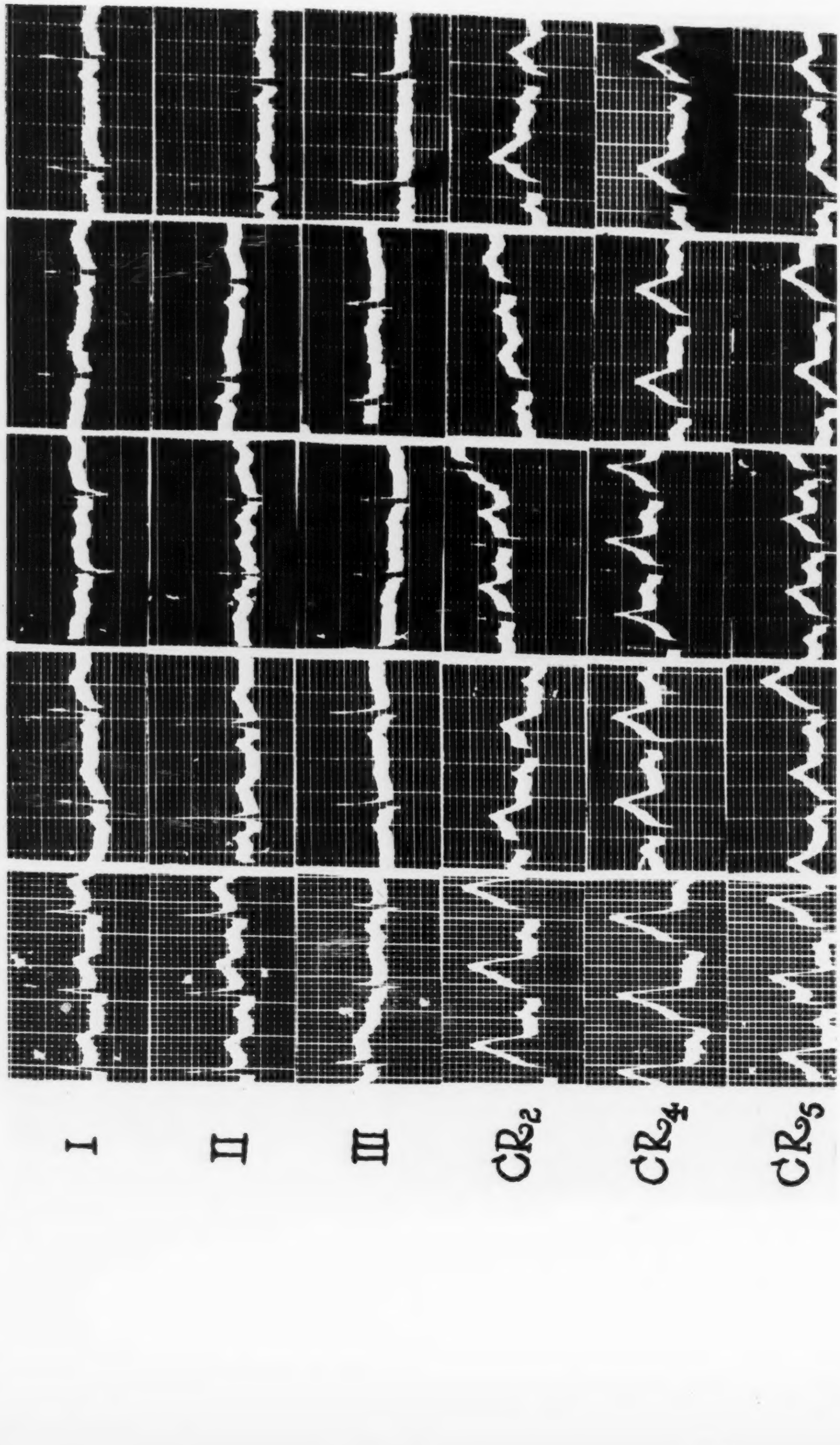
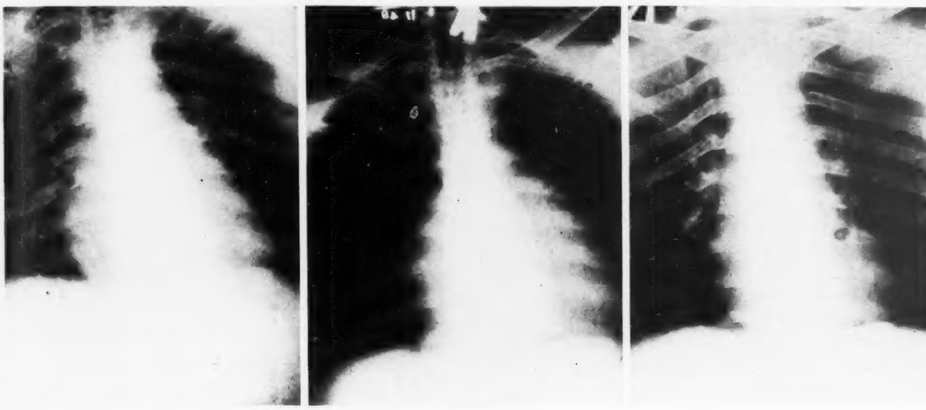


FIG. 1.—Electrocardiograms of a patient with contusion of the heart. See text for discussion.

pulse rate was 108, and respirations were 48 per minute. A pericardial friction rub was heard along the left border of the heart. The heart sounds were of good quality and the rhythm was regular. No evidence of congestive phenomena was present. An electrocardiogram showed a pattern consistent with acute pericarditis (fig. 1, *A*). It was the consensus that traumatic pericarditis or contusion of the heart had been sustained. Symptomatic treatment controlled the chest pain, and the symptoms and signs of pericarditis diminished rapidly. Serial electrocardiograms, some of which are shown, revealed an evolution of the pattern toward normal, and by January 9, 1948, the process had apparently subsided (fig. 1, *B*).

Meanwhile, because of the severe and extensive trauma to the extremities, immobility of the patient, and the impaired circulation of the right foot, it inconstant systolic friction sound was heard over the fourth intercostal space at the left sternal border. The patient was placed in an oxygen tent and given sedation. Because the per cent of normal time* had been reported daily as within safe levels, only reaching 24 per cent on January 10 and never going below that level, the clinicians were not impressed with the danger of bleeding from hypothrombinemia. However, the signs were such that despite the prothrombin reports the possibility of a hemorrhagic pericardial effusion was considered likely. Accordingly, a transfusion of 500 cc. of fresh whole blood was given as soon as possible and 64 mg. of concentrated vitamin K (Hykinone) were given parenterally. During the next thirty-six hours, the blood pressure remained stabilized in the vicinity of 76/60, and the pulse continued to be weak and rapid. Another transfusion was given on January



12/31/47 A — 1/11/48 B — 1/28/48 C

FIG. 2.—Bedside anteroposterior chest x-rays of a patient with contusion of the heart.

was considered that in spite of the pericarditis the threat of thromboembolic complications was of sufficient moment to indicate prophylactic anticoagulant therapy. Dicumarol was accordingly begun on December 31, 1947 and a total of 700 mg. was given in the dosage shown in table 1.

Shortly after 1:00 A.M., on January 10, 1948, there was a sudden onset of severe substernal pain with rapid respiration. On examination, the blood pressure was found to have dropped to 70/40. The pulse was 130 per minute, paradoxic in type, and thready in character. There was mild cyanosis of the nail beds and mucous membranes. The neck veins were slightly distended. Examination of the chest revealed an area of dullness and bronchial breathing below the scapula. The area of cardiac dullness extended 6.0 cm. to the right and 10 cm. to the left of the midsternal line. The heart sounds were distant, and an 11 and parenteral vitamin K was continued at intervals for a total of 256 milligrams. A portable chest x-ray showed the cardiac silhouette to have a globular appearance (fig. 2, *B*), and an electro-

*Prothrombin activity was reported in this hospital, as it still is in many, in terms of "percentage of normal" (straight line curve based on direct relationship between prothrombin times of patient and control). It is now recognized that dependence on reports which are based on this type of curve is fraught with serious danger as this case illustrates. A logarithmic curve such as that recommended by Quick should be used. When the prothrombin times, per se, are not included in the reports to the ward, as was the situation here, the clinician is left without protective check in arriving at a proper interpretation of the results.

cardiogram revealed findings consistent with tamponade (fig. 1, *C*). Urinalysis on January 11 showed innumerable red blood cells, whereas there were none in the five previous daily specimens.

Because there had been a minimal response to conservative measures, an increasing distention of the neck veins (antecubital venous pressure, 260 mm. of water), an increasing pulse rate, and because of the fact that the prothrombin time had reached 57 per cent of normal, it was decided that pericardial aspiration should be attempted. Although there was an obvious risk of serious hemorrhage, the imperative necessity of relieving cardiac compression forced this decision. Accordingly, at 7:00 P.M. on January 11, a pericardial paracentesis was done, and 380 cc. of dark, nonclotting blood withdrawn. There was immediate and dramatic improvement, all signs of cardiac tamponade subsiding rapidly. The pulse rate decreased to 92 and became stronger, the blood pressure rose to 112/70, the respiratory rate decreased, and the heart sounds improved in quality, all within ten minutes' time. On the following day, an electrocardiogram showed reversion to the previous configuration (fig. 1, *D*), the prothrombin time increased to 75 per cent of normal and the urine was free of red blood cells. Thereafter, the cardiovascular status remained essentially unchanged, and a chest x-ray on January 28 revealed the heart to have an essentially normal appearance (fig. 2, *C*). Except for a guillotine amputation of the right foot on February 16 and a hepatitis in April (considered homologous serum in type), the patient made an otherwise uneventful recovery. Favorable progress continued and patient was discharged on September 28, 1948 to a convalescent hospital.

Comment

In the present case the multiple and severe injuries accompanied by severe shock occupied the attention of the staff until life-saving measures had been carried out and immobilization procedures were completed. Attention was first directed to the cardiovascular system when the patient developed precordial pain, a pericardial friction rub, and typical electrocardiographic changes of pericarditis.

Although there was a period of nine days following injury before the appearance of clinical features suggesting involvement of the heart, it was considered that the pericarditis was on a traumatic basis and that there was significant contusion of the myocardium itself. White and Glendy,[20] Barber,[21] Sigler,[22] and others have pointed out that a definite latent period may exist between the trauma and appearance of symptoms and signs of cardiac involvement. White and Glendy[20] have further pointed out that the delayed appearance of pericarditis following trauma suggests the presence of underlying primary damage to the myocardium. The studies of Noth and Barnes,[23] Katz,[24, 25] Bellet and McMillan,[26] White,[27] and others[28-31] have shown that RS-T segment elevations are on the basis of subepicardial myocardial injury. Thus, the electrocardiographic changes in this case would seem to support the diagnosis of myocardial contusion.

Certain individual features of the electrocardiograms in this case are of interest and somewhat uncommon. The usual pattern of injury involving the subepicardial myocardium is characterized by T-wave reversal following initial RS-T segment elevations.[25, 26, 28, 29] In the tracings under consideration the minor T-wave alterations in the limb leads and the absence of T-wave reversals in the precordial leads could not be adequately explained. Bellet and McMillan[32] record that in pericarditis, the stage of RS-T elevation may change into normal upright T waves without passing through the stage of inversion. Nay and Boyer[33] have observed the occasional absence of T-wave inversion in established cases of pericarditis, and Logue and Wendkos[34] have suggested that the stage of T-wave inversion may be missed unless frequent, repeated tracings are taken. This point is worthy of consideration since the RS-T segment changes in our case constituted the only diagnostic pretamponade electrocardiographic feature. The fact that such can be the case serves to re-emphasize the importance of obtaining early and serial electrocardiograms in any case of serious injury in which trauma to the heart should be considered and looked for.

Another interesting electrocardiographic variation was observed in the tracing recorded following the tamponade (fig. 1, *C*). The sudden shift in electrical axis to the right would suggest acute cor pulmonale; however, the other usual features were absent. Gardberg and Ashman[35] have indicated that other conditions causing dilatation of the right ventricle can produce this pattern. Sigler[22] mentioned that shifts in electrical axis may accompany cardiac trauma, and in a case report by Reed and

Berger[36] sudden shift of electrical axis to the right occurred several times and was ascribed to mild right strain.

Our experience with one method of reporting prothrombin activity was particularly distressing. It was at first difficult to understand why hemorrhage should occur in this patient when the prothrombin activity was reported to be within the safe range. At that time, the prothrombin time was being determined in our laboratory by the Quick method,[37] and was reported to the clinicians in terms of percentage of normal in accordance with the formula reported by Diggs.[38] At a later date, when it was realized that our method might be faulty, the procedure was reviewed, and prothrombin levels were recalculated in percentage of normal prothrombin activity (table 1), utilizing the Quick formula and making the necessary correction for difference in thromboplastin. It was then learned that the percentage of prothrombin activity had fallen to dangerous levels approximately sixty-five hours prior to the onset of manifestations of tamponade.

The practice of reporting prothrombin in terms of "percentage of normal" based on a direct time relationship between patient and control (straight line curve) has evidently been in common, though erroneous usage. This has been criticized by Barker and associates[1] and by Wright and Foley.[39] Review of the literature fails to reveal any sound basis for the use of such a method of reporting when the Quick method, or its modifications, is employed for determination of plasma prothrombin time. The bedside whole blood technic of Smith and associates[40] does employ the formula:

$$\textit{Clotting activity (in percentage of normal)} = \frac{\textit{Clotting time of normal control}}{\textit{Clotting time of patient}} \times \textit{100 (linear curve)}$$

However, the assigned critical values differ greatly from those generally applicable to plasma method, that is, the danger of hemorrhage below 10 per cent prothrombin in plasma methods, and below 40 per cent in the bedside technic. Apparently this formula has been applied directly to plasma determinations,[38] without due consideration of differences in technic in interpretation of results. This experience serves to re-emphasize that patient prothrombin levels should be recorded either directly in seconds as recommended by Wright and Foley[39] or as percentage of prothrombin activity by the methods recommended by Barker and coworkers,[1] Fisher,[41] or Quick.[37]

Table 1.—*Comparative Values of Prothrombin Activity in Response to Dicumarol Administration*

Date	Dicumarol in Mgm	Control Prothrombin time*	Patient Prothrombin time*	% of normal time†	% Prothrombin Activity‡
		sec	*sec*		
Dec. 31, 47	300	16	16	100	100
Jan. 1, 48	—	15	30	50	16
Jan. 2, 48	50	16	22	72	33
Jan. 3, 48	50	16	24	65	27
Jan. 4, 48	50	16	26	61	23
Jan. 5, 48	50	16	33	45	15
Jan. 6, 48	100	16	27	59	22
Jan. 7, 48	50	16	37	43	12
Jan. 8, 48	50	16	50	32	8
Jan. 9, 48	—	16	57	28	6
Jan. 10, 48	—	19	79	24	5
Jan. 11, 48 A.M.	—	15	40	37	11
Jan. 11, 48 P.M.	—	15	26	57	22
Jan. 12, 48	—	15	20	75	39
Jan. 15, 48	—	16	19	84	50

Quick method for prothrombin time used.

* Data available in permanent laboratory records but not included on the report to the clinician at that time.

† Calculated by formula previously used. See comment for details.

‡ Data recalculated at a later date (Quick's formula).

Discussion

Study of the present case brings into direct relationship two seemingly unrelated subjects: contusion of the heart due to nonpenetrating trauma of the chest and the increased risk of bleeding associated with administration of anticoagulants. It is now well established that myocardial damage resulting from nonpenetrating injuries to the chest is often compatible with life.[20, 21, 42, 43] Such damage may be present even though visible evidence of known chest trauma is lacking,[20, 21, 44, 45] or as an indirect result of distant severe injuries.[22] Likewise, the risk of bleeding inherent in anticoagulant therapy is

also well established (see introductory remarks). Several observers have recently suggested other situations in which there is an added risk: Herrmann,[46] active pulmonary tuberculosis; Duff and Shull,[9] severe hypertension with cerebral manifestations; Wright,[11] following prostatectomy, and we propose yet another in this report.

The possible presence of traumatic pericarditis and myocardial contusion has not received too serious consideration as an added risk in the exhibition of anticoagulants. The fact, therefore, that the hemopericardium which developed in our case in the absence of cardiac rupture, was associated with anticoagulant therapy appears to be of significance.

In evaluating the possible relationship of increased bleeding tendency associated with dicumarol and the cardiac tamponade, the factor of an independent source of bleeding occurring as a result of softening of the myocardium during evolution of the contusion must be considered. Delayed hemorrhage into the pericardial sac following nonpenetrating injury to the heart can occur. Sometimes this is due to delayed rupture from progressive weakening of the myocardium[20, 21] or to seepage from an injured coronary vessel.[47] More often it is due to extravasation of blood from the damaged tissue[48] or to laceration of the myocardium itself.[20, 21, 44] Beck[49] has emphasized that hemopericardium occurring with contusion is associated with myocardial disorganization which is most marked during the second week following trauma, a point which correlates well with the onset of hemorrhage in this case.

The question arises, therefore, as to whether or not the hemorrhage noted in this case would have occurred if dicumarol had not been used. It is obviously impossible to answer this question. However, we are convinced that dicumarol was a contributing factor to the hemorrhage because of (1) the markedly reduced prothrombin activity of the blood prior to the manifestations of acute tamponade (table 1), and (2) the concomitant appearance of another hemorrhagic manifestation, hematuria. Those are regarded as valid evidence that the tamponade was, at least in part, a consequence of hypoprothrombinemia due to dicumarol. With regard to pathogenesis, we concur in Wright's[11] suggestion, that even though some small degree of independent bleeding may have occurred during the preliminary phases, the major hemorrhage was incident to myocardial and pericardial softening during the evolutionary period, at which time the effect of dicumarol left the ends of small blood vessels inadequately sealed by protective clotting and allowed the occurrence of a massive hemorrhage.

It would seem justifiable, therefore, to call attention to the possible danger of cardiac tamponade associated with the administration of anticoagulants to patients who have received trauma to the heart. It also seems wise to consider that the employment of anticoagulants when indicated in such cases should be undertaken as a calculated risk, and that special caution should be exercised during their administration. The importance of recognizing the presence of trauma to the heart in any case of severe injury is therefore evident.

Conclusions

1. Cardiac tamponade may result from the administration of anticoagulants to patients having nonpenetrating injuries of the heart.

2. Added caution should be observed in the employment of anticoagulant drugs in the treatment of patients having evidence of cardiac trauma.

3. A standardized method of reporting prothrombin activity should be authoritatively settled upon by the leaders in the field of anticoagulant therapy and adopted by the medical profession.

4. Pending general agreement on this point, prothrombin activity should be reported either in terms of seconds or in percentage of activity, using the Quick method of calculation. In either case an added protection consists of including in the report to the clinician the control readings for that day in terms of seconds.

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